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SUPPLEMENTUM 448

EPSILON-AMINOCAPROIC ACID (E-ACA) AS A THERAPEUTIC AGENT BASED ON 5 YEAR'S CLINICAL EXPERIENCE

by

INGA MARIE NILSSON, LENNART ANDERSSON
and SVEN ERIK BJÖRKMAN

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Epsilon-Aminocaproic Acid (E-ACA) as a Therapeutic Agent Based on 5 Year's Clinical Experience[1]

By Inga Marie Nilsson, Lennart Andersson and Sven Erik Björkman

[1] This investigation was supported by grants from the Swedish Medical Research Council, the Swedish Cancer Research Foundation, and from the National Institutes of Health, Public Health Service (Research Grant HE 07066)

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Supplementum 448

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Introduction

The antifibrinolytic effect of epsilon aminocaproic acid (E-ACA) was first described by Okamoto and coworkers (130). Ablondi et al (2) and Alkjaersig et al (7) showed in in vitro experiments that the effect of the substance is due mainly to its inhibition of the activation of plasminogen to plasmin, while its antiplasmin activity is weak.

The first clinical experiments were performed by Japanese researchers (67, 73, 107 108 131 146 172 173) who reported the substance to be effective in the treatment of vomiting of pregnancy, dysmenorrhoea, threatening abortion and various allergic disorders.

Nilsson, Sjoerdsma and Waldenström (125) gave E-ACA to three patients with increased fibrinolytic activity in the plasma, and they found that the activity became normal. They also studied the metabolism of E-ACA in human beings and found that the substance was readily absorbed from the digestive tract; and that when given orally or intravenously it was rapidly excreted by the kidneys. It must therefore be given at fairly short intervals in order to be effective. They recommended a dose of 3—6 grams every 4—6 hours. McNicol, Fletcher, Alkjaersig and Sherry (100) also carried out pharmacological studies of E-ACA. According to these authors the plasma concentration of the drug should be maintained at about 13 mg per 100 ml (10^{-3} M) in order to control systemic fibrinolytic activity. They reported the renal clearance of E-ACA at this therapeutic level to be approximately 75 % of that of the creatinine clearance.

Andersson and Nilsson (18) showed that fibrinolytic bleedings in patients with prostatic cancer and other diseases of the prostate can be treated successfully with E-ACA. Andersson (10, 11, 12) reported that E-ACA can control urinary tract bleeding also in diseases other than prostatic cancer, even in cases without associated increased fibrinolytic activity in the circulating blood.

In 1961 Nilsson, Björkman and Andersson (119) described their clinical experience with E-ACA in the treatment of 57 patients. Since then the substance has been used in various countries of the world in the treatment of a wide variety of haemorrhagic states and has been the subject of many publications (3 4 5 10 13, 14, 15 16 61 69 80b, 82, 86 87 88 99 102 133 143 144 145 148, 170 and others). Most of these reports are based on relatively small series of patients. In a recent review Sweeney (164) stated that even a cursory survey of the literature revealed that more than 1000 patients have received E-ACA.

Though wide experience has thus been gained in the use of E-ACA, its clinical value as an inhibitor of fibrinolysis as well

Methods and Materials

Coagulation analyses. The methods for collection and preparation of blood, and for measuring the different coagulation factors have been described elsewhere (20, 114, 120, 121, 123, 124).

In most patients blood samples were withdrawn before and at various intervals after administration of EACA for determination of the fibrinolytic activity and fibrinogen level. The blood was assayed for fibrinolytic activity by determination of (a) whole blood clot lysis time, (b) plasma euglobulin clot lysis time, (c) the activity of plasma and of resuspended euglobulin precipitate on unheated and heated bovine fibrin plates (123).

Various coagulation factors and the platelet count were determined in patients with bleeding disorders, blood disorders, liver cirrhosis, gynaecologic and obstetrical bleedings, essential haematuria, postoperative bleeding and during operation with extracorporeal circulation.

EACA dosage. A commercial preparation, Epsikapron® (Kabi, Stockholm), was used. When the drug was given intravenously a 10 per cent sterile solution in saline was infused within a period of 10—30 minutes. When administered orally the drug was given in a syrup containing 200 mg per ml or as a granulate. Unless otherwise stated the patients received a dose of 0.1 g per kg bodyweight every 4—6 hours.

as its possible side-effects are still the subject of debate. Particularly the fear of stimulating intravascular precipitation of fibrin and thereby producing or promoting thrombosis has caused many physicians to refrain from using E-ACA. Opinions also differ on the most suitable dosage level.

We have used E-ACA widely during the last five years and therefore consider it legitimate to report our experience from 744 patients treated with this drug. For the sake of simplicity we have divided our material according to the specialities within which the diseases fell.

Methods and Materials

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Table I Surgical cases

Diagnosis	Number of patients	Bleeding symptoms	Number of patients with fibrinolysis	Dosage of EACA g/24 hours	Dosage of EACA total amount g	Effect on bleeding	No effect on bleeding	[illegible] effects	Thrombo-embolism	Deaths
Endothoracic operations	7	Wound bleeding	—	5—35	5—76	7	—	—	—	—
Cardiac operations with extracorp. circ.	21	Wound bleeding in 2	10	5—20	5—20	1	1	—	—	5
Op. of portal hypertension	2	Wound bleeding	2	10 30	10, 60	2	—	—	—	1
Gastric resection for ulcer	1	Wound bleeding + melaena	—	5	5	1	—	—	—	—
Ext. of maxillary cancer	1	Nose bleeding	1	25	80	1	—	1	—	—
Appendectomy	1	Wound bleeding	1	25	70	1	—	—	—	—
Parotidectomy	1	Wound bleeding	—	12—24	36	1	—	—	—	—
	34									

Surgical Cases *Table I*

E ACA was given to 34 patients with diffuse bleeding from the operative field in connection with various surgical procedures (*thoracic surgery, laparotomy, pa*rotidectomy or operation for maxillary cancer) In only 14 of these patients was the fibrinolytic activity in the circulating blood increased

Twenty-one patients received E-ACA during cardiac operations with extracorporeal circulation (Kay Cross disc heart-lung machine) Ten of these patients showed an increased fibrinolytic activity and low fibrinogen values after the perfusion All the patients were given one dose of E ACA intravenously after the perfusion In 2 patients with a high fibrinolytic activity a second dose was given after 3—5 hours Bleeding occurred in only 2 of the 21 patients In one of them another dose of E-ACA promptly stopped the bleeding, but it had no effect in the other patient, who bled from a ruptured vessel and died The other postoperative deaths were due to circulatory insufficiency

Two patients with liver cirrhosis bled diffusely from the wound during the latter part of an operation for establishment of a shunt The fibrinolytic activity in the circulating blood was increased The bleeding stopped promptly after administration of E ACA One of these patients died 8 days after the operation from respiratory insufficiency and widespread bronchopneumonia

One patient had severe haemorrhage after exstirpation of a maxillary cancer and the bleeding recurred in spite of repeated attempts of surgical haemostasis The fibrinolytic activity in the plasma was found to be high When the patient was given E ACA intravenously the bleeding stopped rapidly

One patient with fibrinolysis and bleeding from the wound after appendectomy has been published elsewhere (17)

It is clear from the table that E-ACA had a favourable effect on the bleeding not only in the patients with increased fibrinolytic activity, but also in the patients not showing increased fibrinolysis in the circulating blood except in one patient in whom the bleeding was due to a ruptured vessel

Table II *Urological cases*

Diagnosis	Number of patients	Bleeding symptoms	Number of patients with thrombolysis	Dosage of E-ACA g 24 hours	Dosage of E-ACA total amount g	Effect on bleeding	No effect on bleeding	Mild or side effects	Thrombo embolism	Deaths	Causes of death
Prostatic cancer	52	Haematuria	5	12—40	24—794	48	4	29	2	1	Metastases Pyonephrosis
Prostatic cancer	3	General bleedings	3	5 20 40	40 71 392	3	—	1	1	1	Uraemia, thrombosis coronary infarction
Prostatic cancer	3	—	3	20—40	50—505	—	—	—	—	—	
Prost hyperplasia	130	Haematuria	8	9—40	9—1019	115	15	16	6	1	Uraemia obturating coronary arterio sclerosis and myocardial infarction
Prost hyperplasia	2	Haematuria + general bleedings	2	30	477 540	2	—	2	—	—	
Prostatectomy	250	Haematuria		3—40	14—245	250	—	22	15	1	Bleeding gastric ulcer
Needle biopsy of prostate	14	Haematuria	—	12—20	24—100	13	1	2	—	—	
Polycystic kidney	1	Haematuria	—	8	16	1	—	1	—	—	
Chronic nephritis	1	Haematuria		14	14	—	1	—	—	—	
Renal haematuria (so called ess haematuria)	13	Haematuria	—	9—35	24—1100	11	2	1	—	—	
Cancer ves urin	35	Haematuria	—	12—20	40—142	13	22	12	—	—	
Telangiectasies in the bladder after radio therapy for cancer	2	Haematuria	—	[illegible] 35	20, 63	—	2		2	2	1) Uraemia + coronary infarction 2) General arterio sclerosis + multiple mesenterial emboli
Closure of vesicorectal fistula	1	Haematuria	—	20	43	1	—	1	—	—	
Various operations on the urinary bladder	[illegible]	Haematuria	—	9—25	27—200	18	4	5	—	—	
	529										

Urological Cases *Table II*

526 patients with urinary tract bleeding of varying origin and 3 patients with cancer of the prostate but without bleeding received E-ACA Of the 529 patients, the spontaneous fibrinolytic activity in the circulating blood was increased in 21, including 11 with cancer of the prostate and 10 with benign prostatic hyperplasia Three of these patients with cancer and 2 of those with hyperplasia had generalised haemorrhages (subcutaneous, subconjunctival, gastrointestinal and possibly also intracranial), while 13 had haematuria only In 3 cases of prostatic cancer the fibrinolysis had caused no haemorrhages but was observed on routine studies which we include in the investigation of all patients with this disease In 20 of these patients the fibrinolytic activity became normal immediately after the treatment, while the activity in one case — a man with prostatic cancer and widespread metastases but without bleeding — did not respond to E-ACA In all the cases with haemorrhages the bleeding ceased as soon as the fibrinolytic activity became normal

In the aforementioned cases the dose was, as a rule, 0 1 g per kg bodyweight 5 times a day When the patient s condition allowed, the preparation was given by mouth, otherwise intravenously

In most (508) of the cases the spontaneous fibrinolytic activity in the circulating blood was not increased In all these cases the haemorrhages were confined to the urinary tract The favourable effect of E-ACA must be ascribed to inhibition of local fibrinolysis in the urinary tract This holds true also for prostatectomized patients in whom the fibrinolytic activity in the circulating blood increases during operation but only transiently, and rarely has more than an insignificant enhancing effect on the loss of blood (20)

The urine contains a plasminogen activator, urokinase, which initiates a breakdown of blood clots and thus sustains bleedings of all types in the urinary tract (10, 11) After prostatectomy the urine drains across the raw walls of the prostatic cavity and dissolves the clots sealing the vessels with increased postoperative bleeding as a result The healing of small ulcerations in the inflammatory hyperaemic mucosa of the base of the bladder in prostatic hyperplasia is retarded by the fibrinolytic activity of the urine, and so are bleeding ulcerations in the kidneys e g in local pyelonephritis, polycystic kidney disease and in traumatic renal injury E ACA given intravenously or by mouth is excreted largely unchanged through the kidneys (125) and therefore effectively inhibits the fibrinolytic activity of the urine

E-ACA was given to 250 patients after prostatectomy In most cases the dose was 20—25 g i v a day on the first 3 days after operation and then 9—12 g a day by

Case 1 A 74 year old man with cancer of the prostate and widespread metastases had severe haematuria which made operation necessary It was not possible surgically to stop the diffuse bleeding from the prostate A bladder fistula was established N P N 90 mg/100 ml The patient was given E ACA intravenously in a dose of 6 g five times daily—total dose 66 g Diarrhoea occurred during treatment. Bleeding stopped but the N P N increased successively to 168 mg/100 ml and the patient died 5 days after the end of treatment.

Postmortem examination revealed large widespread metastases pyonephrosis and pulmonary oedema.

Case 2 The patient was an 88 year old man who had 2 years previously been subjected to gastrectomy because of gastric cancer No metastases were known to exist. Extraction of a tooth on August 15 1961 was followed by obstinate bleeding for which he was admitted to hospital Despite attempted surgical haemostasis the bleeding continued and spread to the cheek The patient also developed subcutaneous haematomas on the trunk and arms On August 16 the coagulation time in glass tubes was 5 minutes and the platelet count 226 000 per cu mm Blood transfusions were given On August 17 the blood did not clot not even after addition of thrombin in excess—the patient thus had afibrinogenaemia The fibrinolytic activity was not studied in this case On August 19 the platelet count was 67 000 per cu mm. From August 18 the patient was treated with E-ACA intravenously in a dose of 5—15 g daily total dose 40 g and human fibrinogen in a total dose of 7 g During this treatment the bleeding stopped and the fibrinogen level remained stable above 0 30 g/100 ml But on August 17 the patient developed oliguria and on August 18 he became anuric. After temporary improvement he became worse and died on August 23rd

Postmortem examination revealed prostatic cancer which had not been diagnosed *intra vitam* but no metastases Widespread fibrin thrombosis of the glomeruli and tubular necrosis were seen in both kidneys A fibrin thrombus was found in a pulmonary vein and a fresh thrombus in a coronary artery

Case 3 The patient was an 87 year old man with a markedly hyperplastic prostate and 3 years history of dysuria He was admitted to hospital because of acute retention Attempted catheterization of the urethra failed and suprapubic drainage was established by bladder puncture. The urine was severely blood stained The fibrinolytic activity in the plasma was increased (292 mm² on unheated plates 111 mm² on heated plates) N P N 63 mg/100 ml The patient was given E-ACA in a dose of 4 g five times daily total dose 60 g The fibrinolytic activity became normal and the urine became clear Treatment produced side effects in the form of orthostatic symptoms

One day after the end of this treatment the bladder drain slipped out and a new fistula was established surgically After operation the patient had fever (40 5° C) his general condition deteriorated and he died 4 days after the operation

Postmortem examination revealed widespread arteriosclerosis with coronary stenosis as well as an infarction of the lateral wall of the left ventricle. The pronounced prostatic hyperplasia had caused bladder diverticula and bilateral hydronephrosis

Case 4 A 77 year old man with arteriosclerotic heart disease and auricular fibrillation had one year previously been operated upon because of infiltrating cancer of the urinary bladder The tumour was coagulated with diathermy and the patient was given external radiotherapy with Cobalt 60 Subsequent cystoscopy during follow up revealed no tumour in the bladder but teleangiectasis.

Owing to the severe bleeding of the bladder the patient was admitted to hospital on June 5th 1961 The clot was removed cystoscopically A urethral catheter was inserted and the bladder was irrigated The patient had fever (40 3° C) The plasma fibrinolytic activity was normal The patient was given E-ACA by mouth from 6th to 8th of June in a total dose of 63 g The bleeding subsided but did not stop On June 9 the bleeding teleangiectatic lesions were coagulated cystoscopically The bleeding then ceased. Two days later the patient developed peritonitis and laparotomy revealed multiple intestinal infarctions The patient died at the end of the operation

Postmortem examination showed widespread arteriosclerosis hypertrophy and dilatation of

mouth until the urine became macroscopically clear This treatment reduced the postoperative loss of blood to about one fifth (91 ml), compared with the bloodloss (494 ml) in a control series (10, 14, 15)

Two hundred of the prostatectomized patients received postoperative treatment with heparin—usually in a daily dose of 15,000 I U given subcutaneously and divided in two doses—combined with E-ACA-therapy Treatment with heparin did not increase the postoperative loss of blood, but the frequency of clear or suspected thromboembolism was only 1 % as compared with about 20 % in a control series that had not received anticoagulation therapy (16) One patient in the prostatectomized group died postoperatively in bleeding from a gastric ulcer This patient had received heparin

E-ACA was given by mouth to 14 patients who developed haematuria after perineal puncture biopsy of the prostate The bleeding ceased except in one case where an arterial lesion in the base of the bladder made it necessary to operate upon the urinary bladder and ligate the vessel

E ACA usually had a good effect, also in the treatment of spontaneous haemorrhage in the prostatic region both in hyperplasia and in cancer, as is apparent from the table On the other hand, its effect on bleeding from cancer of the urinary bladder was less regular—in only 13 of 35 cases did it control the bleeding Neither had E-ACA any effect in 2 cases in which the bleeding was due to teleangiectatic changes in the bladder after irradiation therapy of malignant tumours In some cases originally suspected of being bladder tumours and in which the bleeding rapidly ceased on treatment with E-ACA the cause of the bleeding proved to be prostatic hyperplasia

E-ACA was given to 23 patients with continuous bleeding obstructing the drainage of the bladder after operations of various types on the urinary bladder In 19 cases bleeding decreased markedly during this treatment, but produced at most a dubious effect in the remaining 4 cases

E-ACA was given to 15 patients with gross haematuria where the source of bleeding was situated in one of the kidneys — polycystic kidney disease, chronic nephritis, local pyelonephritis, traumatic renal injury with prolonged bleeding or essential haematuria (11) In 12 of the cases the bleeding ceased, in 3 treatment produced no effect (one patient with chronic nephritis, one with renal haemangioma and one with so called essential haematuria)

If the aim is to inhibit the fibrinolytic activity in the urinary tract only, it is possible to use a smaller dose than that necessary for inhibiting generalized fibrinolysis because E ACA is concentrated about 70 fold in the urine (100) In recent years we have, as a rule, given 3 g E-ACA 3—4 times daily and found this dose to be satisfactory Treatment is continued until the urine has become macroscopically clear In cases of essential haematuria we have, however, given E-ACA for at least 6 weeks, although the urine had, as a rule, become clear already after a few days' treatment

Andersson (15) found no significant difference in the frequency of postoperative thrombo embolism between the patients who had been treated with E ACA after prostatectomy and untreated controls No such control material series is available for the other groups of patients

Six of the 529 patients treated died during or immediately after treatment These cases are described below

Obstetrical Cases *Table III*

E ACA was given to 11 women with severe bleeding in connection with delivery and to one woman with bleeding after hysterectomy Five of these women had had *abruptio placentae* 3 had bled profusely after an apparently normal delivery and 3 had bled after caesarian section In 6 of the patients the fibrinolytic activity was increased and in 7 the fibrinogen values were low Five to 6 g of E ACA promptly controlled the bleeding in 9 In 2 cases with extremely profuse bleeding it was not possible to administer more than 3 and 4 g respectively, before they died from profuse haemorrhage Postmortem examination revealed no signs of intravascular coagulation In one patient with uterine bleeding after caesarian section, but with no signs of fibrinolysis E ACA had no demonstrable effect

Table III *Obstetrical cases*

Diagn	Number of patients	Bleeding symptoms	Number of pat. with fibrinolysis	Dosage of E ACA g 24 hours	total amount g	Effect on bleeding	No effect on bleeding	Minor side effects	Thrombo-embolism	Deaths
Post partum bleeding	3	Uterine bleeding	1	5—15	5—15	3	—	—	—	—
Abruptio placentae	5	Uterine bleeding	4	3—20	3—20	4	1	—		1
Caesarean section	1	Uterine bleeding	—	5	5	—	1	—	—	—
Caesarean section	1	Uterine+ wound bleed	—	6	6	1	—	—	—	—
Caesarean section	1	Uterine+ diffuse bleed	1	3	3	—	1	—		1
Caesarean section	1	—	—	25	25			—	—	—
Hysterectomy	1	Wound bleeding	—	5	5	1	—	—	—	—
	13									

the heart as well as multiple mesenterial arterial emboli and intestinal infarctions.

Case 5. A man, born in 1909, was operated upon in 1958 for multiple cancer of the urinary bladder. Two areas of the bladder were excised and radioactive tantalum wires were inserted interstitially. After examination revealed no tumour but teleangiectasis in the bladder.

On November 20th, 1961, the patient was admitted to hospital because of haematuria and painful skeletal metastases. No increased fibrinolytic activity in the plasma was demonstrable. *Because of the haematuria he was given E ACA* by mouth in a dose of 5 g four times within 24 hours. But since the patient passed only 50 ml urine on that day (November 23rd to 24th) treatment was stopped. The urine was still severely blood stained.

On November 28th the patient was subjected to operation with removal of a clot from the bladder, and catheters were passed up into both ureters. Large amounts of urine were drained through the catheters. One day after operation the patient suddenly died during an attack of coughing.

Postmortem examination revealed obstruction of both ureters by tumour masses, widespread metastases, generalized arteriosclerosis and a small fresh myocardial infarction.

Case 6. A 70 year old man was subjected to transvesical prostatectomy because of a hyperplastic prostate with a small, highly differentiated adenocarcinoma. Postoperatively the patient was given E ACA intravenously in a dose of 5 g four times daily—total dose 65 g—and from the morning after the operation heparin subcutaneously in a dose of 10,000 I U in the morning and 5 000 I U in the evening. Three days after the operation the patient had slight *haemoptysis. Chest X ray showed a small parenchymal lesion in the lower lobe of the right lung. Pulmonary embolism was suspected and treatment with E ACA was stopped but heparin treatment continued. After a further day the haemoptysis increased. Laryngoscopy showed that blood flowed from the oesophagus and ran down into the trachea. The bleeding was profuse. Despite blood transfusions the patient died.

Postmortem examination revealed a gastric ulcer saturated with blood, and abundant amounts of blood in the stomach, oesophagus, trachea, bronchi and intestines. As far as we knew the patient had not had any symptoms of ulcer before the operation.

Coagulopathies and Blood Disorders *Table V*

CASES WITH COAGULOPATHIES

E ACA has been given to 19 patients with *haemophilia A or B or von Willebrand s disease* in connection with bleeding episodes such as haematuria, gastrointestinal bleeding and wound bleeding following tooth extraction Six of these patients, including 4 with severe haemophilia A and 2 with severe haemophilia B, had massive gross haematuria, which responded favourably to 3—6 days treatment with E-ACA The patients with haemophilia A also received replacement therapy consisting of human fraction I—O (122) but in smaller doses than they had received in earlier episodes of haematuria The patients with haemophilia B who were treated during 5 episodes received no other treatment It is difficult to evaluate the effect of E-ACA in 5 patients with haemophilia A and gastrointestinal bleeding who also received fraction I—O but in 2 of the cases it seems to have helped to arrest the bleeding One patient aged 42 with severe haemophilia B and a circulating anticoagulant has on his own initiative started to take E-ACA immediately he notices any signs of bleeding especially incipient joint bleeding haematuria and haematoma In the course of 18 months he has taken all together 4 773 g of E-ACA During this period he attended high school and had only a few episodes of severe bleeding He reported no side effects whatsoever Liver function tests (GOT GPT, alkaline phosphatase bromsulphalein bilirubin) and E C G during this time revealed nothing remarkable

E-ACA has been given to 10 patients with bleeding disorders in connection with tooth extractions Of these patients, 2 had severe, 1 moderate, and 2 mild haemophilia A 1 had moderate and 2 mild haemophilia B, 1 had v Willebrand s disease, and 1 had thrombasthenia The patients received ordinary replacement therapy besides treatment with E-ACA In preliminary studies we have found the fibrinolytic activity in the extraction alveoli to be increased and probably capable of causing bleeding 3 to 4 days after extraction (31) Treatment with E ACA stopped or suppressed this post extraction bleeding In those patients who were not bleeding at the beginning of treatment no bleeding occurred in the further course either

CASES WITH BLOOD DISORDERS

E ACA was given to 13 patients with leukaemia (acute myeloblastic leukaemia in 12 and chronic myeloid leukaemia in 1) All these patients had bleeding symptoms consisting of gastrointestinal bleeding gingival bleeding epistaxis and haematomas In 7 of these patients the fibrinolytic activity was increased and their fibrinogen values ranged between 0 05 and 0 24 g/100 ml After administration of

Gynaecological Cases

Table IV

We have also given E-ACA to 26 females with profuse menstrual flow but without any demonstrable gynaecological disorder (118). The blood losses had invariably caused iron deficiency anaemia. Eighteen of these patients were otherwise healthy women and 8 had a haemorrhagic diathesis. Of the 18 women with no demonstrable coagulation defect, one was treated during 19 periods, 5 during 5 to 9 periods, and the remaining 12 during 1 to 4 periods. E-ACA reduced the menstrual flow to normal in all but one of the patients. The drug was given orally in a dose of 0.1 g per kg bodyweight, but not until the flow had become profuse, usually on the second day. The amount of E-ACA given during each period varied from 6 to 90 g. Treatment for some periods normalized the haemoglobin level. Two patients became pregnant during treatment and gave birth to normal children. In the 8 patients with haemorrhagic diathesis and profuse menstruation E-ACA alone proved sufficient to normalize bleeding, although some of the patients required rather large doses (75—420 g per period). In [illegible] patients who went into shock owing to the heavy blood loss the response to E-ACA was dramatic. One of these patients was treated during 31 periods and received all together 4,856 [illegible] E-ACA without any side effects.

Table IV *Gynaecological cases*

Diagnosis	Number of patients	Number of periods treated	Dosage of E-ACA: g per menstrual period	Dosage of E-ACA: total amount g	Effect on bleeding: Normalization	Effect on bleeding: No effect	Minor side effects
Profuse menstruation without any demonstrable gynaecologic disorder and with normal coagulation mechanism	18	1—19	6—90	6—340	17	1	13
Profuse menstruation in patients with coagulation defects							
Congenital haemorrh. diathesis with prolonged bleeding time							
Thrombocytopenia	1	31	75—420	4856	1	—	—
Thrombocytopenia + myeloblastic leukaemia	3	2 4, [illegible]	6—150	174, 198, 504	3	—	1
Thrombasthenia	1	1	114	114	1	—	—
Haemophilia C	1	8	60—180	1010	1	—	1
	[illegible]	1, 6	5—15	7, 57	2	—	2
	26						

Thrombasthenia + tooth extraction	1	B eed g f o mvity								
Thrombasthenia + tooth extraction	1	—	—	12	120			—	—	—
Thrombocythaemia	1	Epistaxis	—	6—24	72	—	1	1	—	—
Polycythaemia	1	*Gastrointestinal*	1	24	72	1	—	1	—	—
Aplastic anaemia	1	Gastrointestinal	—	8—25	964	—	1	1	—	—
Leukaemia	13	Haematomas Epistaxis *Gingival* bleed Melaena	7	6—36	6—1440	10	3	6	—	13
	43									

* *No effect* on fibrinogen level

E-ACA to the 7 patients with increased fibrinolytic activity the bleeding stopped or decreased markedly in all except one, who received only one dose of E-ACA a few hours before death The remaining 6 patients received total doses of E-ACA of 42, 152, 246, 360, 432 and 655 g, respectively

In the other 6 patients with leukaemia and without demonstrable fibrinolytic activity in the plasma the bleedings tended to decrease in 5 after E-ACA therapy These 6 patients received total doses of E ACA of 24, 60, 130, 420, 736 and 1,440 g, respectively

Treatment had no demonstrable effect on the actual leukaemia.

All the patients with leukaemia died from their disease Eleven were autopsied None of them showed signs of toxic effect of the drug intravascular coagulation myocardial infarctions or endocardial bleedings

E-ACA was given in a total dose of 964 g to one patient with aplastic anaemia and severe gastrointestinal bleeding, but with no signs of fibrinolysis It had no effect Postmortem examination showed no signs of any toxic effect of the drug

One patient with polycythaemia and gastrointestinal bleeding and high fibrinolytic activity and low fibrinogen value responded favourably to E-ACA

E ACA was given to one patient with thrombocytopenia and one patient with haemorrhagic thrombocythaemia. The drug had no effect

One patient with congenital hypofibrinogenaemia received a total dose of 189 g of E-ACA It had no effect on the fibrinogen value

Table V *Cases with coagulopathies and blood disorders*

Diagnosis	*Number of patients*	*Bleeding symptoms*	Number of patients with fibrinolysis	Dosage of E ACA g/ 4 hours	Dosage of E ACA total amount g	Effect on bleeding	No effect on bleeding	Minor side effects	Thrombo embolism	Deaths
Severe haemophilia A + tooth extraction	2	Bleeding from cavity	—	4, 32	4, 104	1	1	1	—	—
Moderate haemophilia A + tooth extraction	1	—	—	20	80		—	—	—	—
Mild haemophilia A + tooth extraction	1	Bleeding from cavity	—	16	64	1	—	—	—	—
Mild haemophilia A + tooth extraction	1	—	—	24	96			—	—	—
Moderate haemophilia B + tooth extraction	1	Bleeding from cavity	—	20	100	1	—	—	—	—
Mild haemophilia B + tooth extraction	1	Bleeding from cavity	—	18—24	216	1	—	—	—	—
Mild haemophilia B + tooth extraction	1	—	—	24	168			1	—	—
Willebrand's disease + tooth extraction	1	Bleeding from cavity	—	24	72	1	—	1	—	—
Willebrand's disease + tooth extraction	1	—	—	35	105			1	—	—
Severe haemophilia A	3	Gastrointestinal bleed	—	20—30	120—662	3	—	—	—	—
Moderate haemophilia A	1	Colon bleeding	—	10—20	130	—	1		—	1
Mild haemophilia A	1	Gastric bleed	—	5—30	110	1	—		—	1
Severe haemophilia A	4	Haematuria	—	5—36	48, 210	4	—	2	—	—
Severe haemophilia B	2	Haematuria	—	24	120, 264	2	—	2	—	—
Severe haemophilia B	1	Haematuria + gastrointestinal bleed + haemarthros	—	15—30	4773 (5/63—1/65)	1	—	—	—	—
Severe haemophilia B	1	Wound bleeding	—	16	64	1	—	1	—	—
Congen. hypofibrinogenaemia	1	—	—	28	189	*		—	—	—
Thrombocytopenia	1	Epistaxis	—	5—20	25	—	1	—	—	—

revealed no toxic effects of the drug

One patient with *gastric cancer* and widespread metastases was admitted to hospital with signs of widespread thrombosis in the arms and legs and with gangrene of the right foot and left hand as well as generalized mucosal bleeding. Coagulation studies showed signs of intravascular coagulation with thrombocytopenia associated with fibrinolysis. No fibrinogen could be demonstrated. The patient was treated with fibrinogen and E ACA in a total dose of 17 g as well as with heparin. Treatment failed to produce the desired effect and the patient died 2 days after admission. Postmortem examination showed widespread haemorrhages as well as multiple thrombosis in the veins of the head and limbs and in the pulmonary artery. The patient had splenic infarctions and multiple glomerular thrombi in the kidneys. According to the histological examination, the thrombi were about 2 days old – This patient had evidently a defibrination syndrome associated with fibrinolysis. Nothing suggested that the thrombosis had developed during treatment with E ACA since the patient had had multiple thrombosis already before treatment had been started.

Another patient had *pancreatic cancer* with widespread metastases and *gastrointestinal bleeding*. As in the previous case coagulation studies showed signs of *intravascular coagulation and fibrinolysis* (fibrinogen value 0 03 g/100 ml). During the last 24 hours of life the patient was given 24 g E ACA. Postmortem examination revealed diffuse bleeding and thrombi in the lungs, renal vessels and splenic artery. Multiple infarctions had formed in these organs and the thrombi were judged as being older than 24 hours.

E-ACA had no effect on the intestinal bleedings in one patient, in whom the haemorrhages did however, respond favourably to later treatment with Trasylol®. But the patient died and necropsy showed widespread necroses retroperitoneally in the mesenterium and in the intestines. The cause of these lesions was obscure. They may, however, have been due to *acute pancreatitis*. If so, the favourable effect to Trasylol might be explained by the inhibitory action of the substance on trypsin.

As already pointed out in the introduction, Japanese workers have reported E ACA to be effective in the treatment of various skin diseases of allergic origin and also able to prevent allergic reactions. One of our patients with severe *exfoliative dermatitis* received 72 g of E-ACA. No improvement of the condition was observed. E ACA was also given to one patient with severe *bronchial asthma*, but it had no effect on the condition. One patient with flushes believed to be due to bradykinin intoxication received all together 176 g E ACA but without any demonstrable effect.

NILSSON and FLODERUS (127) described a family with *periodic angioneurotic oedema*. One of the members of this family was found to have slightly increased fibrinolytic activity and a decreased AHF value during these attacks. In order to find out whether it was possible to prevent the decrease of AHF we administered E ACA in connection with one attack. The usual decrease of AHF did not occur. In addition the patient reported that his symptoms soon disappeared. He himself then started to take E-ACA immediately at the first signs of incipient symptoms and in this way he was, as a rule, able to control the attacks but only when he started to take E-ACA as soon as the symptoms began to appear. During the last 2 1/2 years he has

Miscellaneous Diseases *Table VI*

E-ACA was given to 3 patients with *cerebral haemorrhage* In [illegible] of them the fibrinolytic activity was increased The drug had no effect on the cerebral haemorrhage

We treated also 9 patients with *liver cirrhosis* Of these, 3 had bleeding symptoms in association with high fibrinolytic activity and low fibrinogen values, and 2 had increased fibrinolytic activity but no bleeding symptoms In the patients with fibrinolysis E ACA suppressed the fibrinolytic activity and the bleedings stopped or decreased Two patients without fibrinolysis bled from oesophageal varices In these 2 cases E-ACA had no effect One patient had no bleeding symptoms and no fibrinolysis Three patients received relatively large total doses, 144, 360 and 753 g, respectively One patient had uraemia and received E-ACA during the last two days of life, when he was completely anuric This patient and 3 others died from their basic disease Postmortem examination revealed no signs of intravascular coagulation

The effect of E-ACA was also studied in cases of *chronic ulcerative colitis* with intestinal bleeding In these patients the fibrinolytic activity in the circulating blood was not increased E ACA controlled the bleeding in all of them It was necessary to give E ACA at intervals of 4 to 5 hours to sustain the effect The bleeding recurred on withdrawal of E-ACA or reduction of the dose In all these patients, however, E-ACA, whether given intravenously or by mouth, produced side effects in the form of nausea and diarrhoea and was therefore discontinued

E ACA was also given to 8 patients with *acute gastrointestinal bleeding* (duodenal ulcer, unknown aetiology, Henoch Schonlein's purpura) In none was the fibrinolytic activity in the blood increased Only 2 of these patients received large amounts (75 and 580 g totally) and in these the bleeding stopped In the other patients, who received only sporadic doses, E-ACA had no demonstrable effect

E-ACA was given to 4 patients with *uraemia and bleedings* (melaena, purpura) but without increased fibrinolytic activity The patients received 1 to 4 doses a day The intestinal bleeding decreased in one of the patients, but not in the other 3 These patients died in uraemia Postmortem examination did not reveal any signs of intravascular coagulation

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Pancreatitis?	1	Intestinal	—	[illegible]	[illegible]						necroses
Exfoliative dermatitis	1	Cutaneous	—	12—[illegible]	72	—	1		—	1	Exfoliative dermatitis
Bronchial asthma	1	—	—	20	20	*		—	—		
Angioneurotic oedema	1	—	1	4—28	5131	**		—	—	—	
Flushes	1	—	—	8—12	176	***		—	—	—	
	42										

* No effect on asthma
** Improvement of disease
*** No effect on flushes

taken E ACA in association with 79 attacks, every time 7—133 g During this time he has taken all together 5131 g E ACA He has not had any side reactions at all Liver function tests (GOT, GPT, bromsulphalein, bilirubin) gave normal values

Table VI *Miscellaneous diseases*

Diagnosis	Number of patients	Bleeding symptoms	Number of patients with fibrinolysis	Dosage of E ACA g/24 hours	Dosage of E ACA total amount g	Effect on bleeding	No effect on bleeding	Minor side effect	Thrombo embolism	Deaths	Causes of death
Cerebral haemorrhage	3	No other bleeding symptoms	[illegible]	3—56	24—56				—	3	Cerebral haemorrhage
Liver cirrhosis	1	Subcutaneous bleedings	1	1—6	10	1	—			1	Hepatic cancer
Liver cirrhosis	2	Melaena	2	10—24	360, 753	2	—	2	—	—	
Liver cirrhosis	[illegible]	Oesophageal bleeding	—	24	24, 144	—	[illegible]	1	—	1	Oesophageal bleeding
Liver cirrhosis	2	—	2	4.5—6	6, 10, 5						
Liver cirrhosis + uraemia after portacaval anastomosis	1	Gastrointestinal	—	30	90	—	1			1 1	Hepatic cancer Uraemia + bleeding
Biliary cirrhosis	1	—	—	5	5			—	—	—	
Hodgkin's disease	1	Gastrointestinal	1	4—10	42	1	—	—	—	1	Hodgkin's disease
Ulcerative colitis	7	Intestinal	—	8—25	12—216	7	—	7	—	—	
Gastrointestinal bleeding of various aetiology	8	Gastrointestinal	—	4—25	6—580	4	4	—	—	—	
Uraemia	4	Melaena, purpura	—	6—20	18—280	1	3	4	—	4	Uraemia
Fallot's tetralogy	1	Pulmonary, tracheal	1	6	6	—	1		—	1	Pulm. bleeding
Staphylococcal sepsis	1	General	—	11	11	—	1			1	Sepsis
Bronchial cancer	1	Pericardial	—	18	18	—	1		—	1	Pericardial bleeding
Disseminated gastric cancer + defibrination	1	General	1	17	17	—	1		1	1	Bleedings + dis

Table VII Induced fibrinolytic states

Diagnosis	Number of cases	Bleeding symptoms	Other symptoms	Number of ... and ...	Dosage of EACA: g 24 h ...	Dosage of EACA: total amount ...	Side effects	Comments
Infusion of Pyrexal to normal persons	3	—	Fever	3	14 18 18	14 18 18	—	No effect on fever ... fibrinolysis
Meprobamate hypersensitivity	1	—	Shock	1	12	12	—	No effect on shock. Fibrinolytic activity normalized
Infusion of SK+EACA to patients with femoral neck fracture (thrombosis prophylaxis)	10	—			4.5—30	4.5—30		
Infusion of SK+EACA to patients with various thrombotic states	43	—						
	57							

As reported in a previous paper (119), we studied the effect of E-ACA in one female patient known to be hypersensitive to Meprobamate® E ACA inhibited the fibrinolytic activity which developed in connection with the anaphylactic shock, but it had no effect on the shock itself We have also studied the effect of *pyrogens* given first alone and then together with E-ACA in 3 normal subjects E-ACA did not influence the fever response or the haematological changes (leukopenia, eosinopenia) induced by the pyrogens Here, in contrast to what was seen in the patient with anaphylactic shock, E-ACA in a dose of 14 and 18 g did not inhibit the fibrinolytic activity

E ACA has been used as an *antidote to streptokinase* (SK) (47, 53, 131, 156, and others) We administered streptokinase together with E ACA to 43 patients with various thrombotic episodes SK was administered in large doses in accordance with a dosage scheme described by OLOW (132) E-ACA was given in one dose of 0 1 g per kg bodyweight immediately before the streptokinase infusion and then in an equal dose 4 hours later

This series of infusions of SK plus E ACA produced a significant reduction of the alterations in the coagulation factors and plasmin activity compared with the values obtained in a series of infusions of SK alone But the activity recorded on unheated fibrin plates as well as the euglobulin clot lysis time indicated the presence of as high a fibrinolytic activity as when no E ACA was given No bleeding complications occurred in the patients given SK plus E ACA In our series of patients with thromboembolic disorders, of whom 195 received SK alone and 43 SK plus E-ACA, no difference in clinical effect could be observed

and about to undergo shunt operations In a series of 350 patients KUGEL (80 b) studied the effect of E ACA in different types of thoracic surgery A further 350 patients served as controls Postoperative bleeding occurred in only 3 of the patients treated with E ACA, but in 25 of the controls The number of administered blood transfusions in the E ACA group was 39 5 % lower than that in the control series

At operations with the use of extracorporeal circulation fibrinolysis has proved to be a common complication (9, 61 79, 126 166) In our experience the preventive use of E ACA in association with extracorporeal circulation should be considered GANS and KRIVIT (61) also recommended the use of E ACA in open heart surgery They have, like us administered E-ACA at the end of the cardiac by pass WEISS et al (170) and MARCHAL et al (94) also stressed the value of E-ACA in association with extracorporeal circulation SAMAMA et al (145) reported a material of 280 patients, subjected to thoracic surgery with extracorporeal circulation 190 of these received E ACA in a dose of 0 05 g per kg bodyweight given in one intravenous injection after the cardiac by pass They reported no serious side effects and emphasized the absence of thrombosis in their material

As pointed out above (Table 1), we found E-ACA to have a favourable effect on the postoperative bleeding also in cases without increased fibrinolytic activity in the circulating blood DEYSINE and CLIFFTON (46) reported that E ACA was effective in controlling bleeding in 15 of 17 surgical patients most of whom showed no evidence of increased fibrinolytic activity It is of course difficult to judge the effect of the treatment in those cases in which the fibrinolytic activity in the circulating blood was not increased but in which the bleeding ceased or diminished on treatment with E-ACA because such bleeding often ceases spontaneously The favourable response to E-ACA nevertheless indicates that diffuse bleeding from an operative wound may, at least in part, be due to the effect of local fibrinolytic activators

Urology In bleedings with associated increased fibrinolytic activity in the circulating blood in patients with prostatic diseases—carcinoma or hyperplasia—we found E ACA to be a valuable agent In all of our patients with this condition the bleedings ceased during treatment, whether the bleedings were generalized or only confined to the urinary pathways (10 12, 13, 18) Attempts to control the bleeding by surgical method in these situations usually only tended to increase the blood loss

The favourable effect of E ACA on fibrinolytic bleeding in patients with cancer of the prostate has been reported also by other workers in this field (77, 85 93, 157)

In patients with fibrinolysis all surgery, even minor operations such as tooth extraction and appendectomy, is attended by considerable risk of bleeding Since cancer of the prostate is not uncommonly complicated by fibrinolysis (13), patients with this disease should always be examined with regards to fibrinolytic activity in the plasma before they are subjected to operation If the activity is increased the patients should be treated with E ACA both before and during the operation

In the aforementioned situations we recommend a dose of E-ACA of 0 1 g per kg bodyweight 5 times a day by mouth or intravenously

Haemorrhages in the urinary tract can be controlled by treatment with E-ACA

General Discussion

Uptil now we have used E ACA as a therapeutic agent in 744 patients and have found the preparation to be a valuable inhibitor of fibrinolytic activity, suitable for routine clinical use

The substance is rapidly and completely absorbed from the digestive tract and is eliminated relatively quickly in unchanged state by the kidneys The preparation must therefore be given in rather large doses at short intervals In the treatment of conditions with increased fibrinolytic activity in the circulating blood we have found a dose of 0 1 g E-ACA per kg bodyweight 5 times a day to be satisfactory

Since E-ACA is concentrated 70 fold in the urine (100), smaller doses can be given if it is considered sufficient, as it often is in haematuria, to inhibit only the fibrinolytic activity in the urinary tract We have found a dose of 3 g 3—4 times daily satisfactory

In antifibrinolytic therapy it is important to give adequate doses In many of the published cases given E-ACA without effect the absence of a response was probably due to insufficient dosage In acute cases, e g postpartum haemorrhage, it is also of paramount importance that the dose should be given intravenously with an infusion period of 10 minutes and not in the form of a slow infusion

On the basis of our experience we consider treatment with E-ACA to be indicated in the following situations

Surgery Acute generalized fibrinolysis in association with operation It is mainly operations on the thorax, pancreas, prostate, liver and female genital tract, that are complicated by fibrinolysis, but fibrinolytic bleeding may occur after any type of operation, even in connection with minor operations such as appendectomy and herniorrhaphy (17, 18, 19, 20, 34, 38, 45, 66, 83, 93, 97, 138, 151, 158, and others) Since such bleedings are often difficult to stanch but can be controlled by treatment with inhibitors of fibrinolysis, it is important that all surgeons should be acquainted with this complication

A good haemostatic effect of E ACA in association with surgical procedures has also been reported by several other authors Operations for portal hypertension (porta caval or spleno renal shunts) are known to be complicated by fibrinolysis and bleeding (84, 96) Grossi, Rousselot and Panke (69) studied the effect of E-ACA in association with the establishment of a shunt in 11 patients with liver cirrhosis Towards the end of the operation bleeding occurred because of increased fibrinolytic activity but was controlled by intravenous administration of 10 g E-ACA According to these authors, treatment with E-ACA at such operations reduces the operative mortality Leger, Lande and Fournet (86) found pre-operative treatment with E-ACA to have a good effect in patients with liver cirrhosis

and tenderness in this region for in such cases there is a fairly large risk that the renal pelvis is partly filled with clotted blood Elimination of the fibrinolytic activity of the urine will probably make the spontaneous passage of such clots more difficult We have never encountered such a complication although some of our patients have had considerable bleeding from the upper urinary tract However, McNicol et al (99) have reported one case and Stark et al (161) 3 cases of urinary bleeding in haemophiliacs where a clot was retained in the renal pelvis Nevertheless, in view of the considerable risk attending operations on patients with coagulopathy E ACA must be regarded as a valuable supplement to conventional substitution therapy in these conditions

In all of these cases where only inhibition of local fibrinolysis in the urinary tract is desired we have found a dose of 3 g 3—4 times daily to be sufficient whether given by mouth or intravenously

Obstetrics and gynaecology We consider it indicated to give E-ACA in *fibrinolytic bleeding states in association with delivery* In ▌ of our patients E-ACA appeared to be life saving In these situations however it is absolutely necessary that the agent is given in adequate amount 0 1 g per kg bodyweight and that the injection is given rapidly (within 10 minutes) Obstetrical cases complicated with bleeding and successfully treated with E-ACA have also been reported by other workers in this field (4 35 143)

According to several authors (6 27 37, 89 109 134 139 141 149 150 153, 168, and others) most obstetrical bleeding symptoms should not be caused by generalized fibrinolysis but by generalized intravascular coagulation (defibrination) with or without associated fibrinolysis It is in our opinion difficult to distinguish between intravascular coagulation and generalized fibrinolysis Both conditions are associated with an increased bleeding tendency and are characterized by a low content of fibrinogen factor V, AHF and plasminogen The prothrombin value and the number of platelets, however, are said to be normal in patients with fibrinolysis but decreased in patients with intravascular coagulation (23, 48) The use of the immunological technique for the demonstration of fibrinolytic degradation products of fibrinogen and/or fibrin is also useful in the diagnosis of these conditions (114) We believe that determination of the plasminogen level can be useful in differentiating between fibrinolysis and intravascular coagulation For we have not been able to verify the findings of Sherry et al (154) and Sawyer et al (147) that plasminogen is deposited in significant amounts whenever a clot forms We thus believe that a low plasminogen value argues for a fibrinolytic state

Merskey et al (105), Lieberman (89) and Sharp (152) have warned against the use of fibrinolytic inhibitors in connection with defibrination syndrome even in the presence of associated fibrinolysis The defibrination syndrome has been reported not only as an obstetrical complication but also in urological diseases carcinomatosis intrathoracic operations and in various internal diseases such as liver cirrhosis sarcoma leukaemia congenital haemangioma septicaemia and purpura fulminans (8 23 26, 29 32 33 58 63 72, 73, 80 a 90 105 110 135 136 137 142 167 168 174) Merskey et al (105) and Lieberman (89) stress that the use of fibrinolytic inhibitors in the abovementioned conditions will further increase the intravascular coagulation process and poten

even in many of the cases where no increased fibrinolytic activity can be demonstrated in the circulating blood As mentioned above, the plasminogen activator in urine, urokinase, tends to sustain all bleedings in the urinary tract E-ACA given by mouth or intravenously is excreted in the kidneys and the activity of the urokinase is thereby inhibited with haemostasis as a result

We have thus found the postoperative loss of blood after prostatectomy to be considerably reduced in patients treated with E-ACA during and after operation (10, 15, 14, 19) Several other authors have also published small series in which they noted a significant decrease in the postoperative loss of blood in patients treated with E-ACA (3, 82, 86, 94, 98, 99, 133, 144, 148)

Such antifibrinolytic therapy after operation of the prostate is of value also because it enables adequate anticoagulation treatment with consequent suppression of the otherwise high frequency of postoperative thrombo embolism In one group consisting of 50 prostatectomized patients treated postoperatively with E-ACA thrombo embolism was diagnosed or suspected in 9 (18 %) In another group of 100 patients given E ACA combined with heparin subcutaneously in a dose of 15,000 I U per day thrombo embolism was suspected in only one (14, 16)

In prostatic cancer, as in benign prostatic hyperplasia, bleeding from the neck of the bladder is not uncommon In such cases, as in troublesome haemorrhage after operations of various types on the urinary bladder, we have found E-ACA to have a favourable effect As mentioned previously, we have found E-ACA to be less useful in the treatment of spontaneous bleedings from carcinoma of the bladder

In the abovementioned haemorrhagic states in the bladder, where it is desired to inhibit the fibrinolytic activity of the urine in the bleeding region, treatment may also be given in the form of continuous instillation of E-ACA into the bladder—5 g E-ACA per 1000 ml solution In most cases, however, such instillation probably has no advantages over oral or intravenous administration

We have found that this type of therapy in the abovementioned cases usually controls the bleedings so effectively that no difficulties occur in the drainage of the bladder If, however, urination is obstructed by persistent clots in the bladder, they should be removed in the usual way by evacuation through semirigid catheters or cystoscopically

Though the main indication for treatment with E ACA in urology is bleeding in the lower urinary pathways, the agent is also useful in the treatment of certain types of renal haemorrhage ANDERSSON (11) and TAMURA, TOFUKUJI, OGAWA and KONO (165) have shown that essential haematuria, i e renal bleeding whose cause remains obscure despite thorough examination, can often be controlled by E ACA Before such symptomatic treatment is started one must, of course, first exclude the presence of tumour, concrement or other urinary tract disease requiring some other type of treatment

Prolonged postoperative (175) or post traumatic renal bleeding, like renal bleeding in patients with haemophilia or other coagulopathies, often responds favourably to E-ACA-therapy Because of the difficulty in removing any obstructing clot from the upper urinary pathways one should probably exercise some caution in the administration of fibrinolytic inhibitors in profuse renal bleeding with severe pain

and tenderness in this region, for in such cases there is a fairly large risk that the renal pelvis is partly filled with clotted blood Elimination of the fibrinolytic activity of the urine will probably make the spontaneous passage of such clots more difficult We have never encountered such a complication although some of our patients have had considerable bleeding from the upper urinary tract However, McNicol et al (99) have reported one case and Stark et al (161) 3 cases of urinary bleeding in haemophiliacs where a clot was retained in the renal pelvis Nevertheless, in view of the considerable risk attending operations on patients with coagulopathy E ACA must be regarded as a valuable supplement to conventional substitution therapy in these conditions

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tiate a thrombotic disorder But these authors appear to base their assumption on theoretical speculations since they have not reported any cases of their own in which inhibitors in such cases had such an unfavourable effect

We (115) have studied cases of ablatio placentae and of several other bleeding symptoms believed to be due to defibrination syndromes In all these cases we have been able to demonstrate fibrinogen degradation products in high titre as well as a decreased plasminogen level, which shows that the so-called defibrination syndrome at least includes a fibrinolytic component We postulate that the fibrinolytic component is of considerable significance in the aetiology of the bleeding in these cases It is a curious fact that patients with congenital fibrinogen deficiency are not particularly prone to bleed, which argues for that a low fibrinogen concentration in itself does not induce bleeding As shown in Table III, we have given E-ACA to several patients without any subsequent complications and with the immediate result that after administration of E ACA the bleeding ceased This is in complete accordance with the idea that the bleeding was due to fibrinolysis and does not suggest that *defibrination as such is mainly* responsible for the bleeding We therefore believe that treatment with E-ACA is indicated in fibrinolytic bleeding conditions occurring in association with parturition whether intravascular coagulation is primarily present or not But in cases with definite evidence of intravascular coagulation in association with fibrinolysis, we consider combined treatment with E ACA and heparin to be indicated This view is also held by SHERRY, FLETCHER and ALKJAERSIG (155)

E ACA has proved *effective in the symptomatic treatment of profuse menstruation*, whether idiopathic or secondary to haemorrhagic disorders (118) In such cases the preparation should not be given before profuse menstruation has started and the examiner has convinced himself that it is an ordinary menstruation and not a bleeding in early pregnancy For, according to toxicity studies by MELANDER et al (103) on rats, the possibility of a teratogenic effect cannot be excluded As in every form of symptomatic treatment E-ACA should not be resorted to until the possibility of uterine cancer or some other gynaecologic disease has been excluded NILSSON (116, 117) and ALBRECHTSEN and SKJODT (5) also reported series of menometrorrhagia, effectively treated with E ACA An alternative to E ACA treatment is treatment with gestagens If pregnancy is desired or if for other reasons gestagens cannot be employed, E ACA is the drug of choice in the treatment of profuse menstrual bleeding in normal women We consider E-ACA indicated in the treatment of profuse and intractable uterine bleeding in patients with haemorrhagic diathesis, *e g* in patients with severe v Willebrand's disease and severe thrombocytopenia We do not consider it indicated *in these cases to place the patients on permanent* E ACA-treatment, but only to use E ACA symptomatically until definite treatment has been decided upon, *e g* hysterectomy or splenectomy

Coagulopathies and blood disorders We have tried E ACA together with conventional substitution therapy in 20 patients with *haemophilia and other bleeding disorders* We do not recommend E-ACA in haemophiliac disorders *per se*, but we feel it may be a valuable supplement to ordinary replacement therapy in bleeding symptoms in which local fibrinolysis is

known to play a role E ACA has no effect on the coagulopathy *per se*, but it inhibits the local fibrinolysis in the bleeding tissue, produced by the tissue activator, which together with the general coagulation defect sustains the bleeding This holds particularly true for bleeding in the urinary tract, uterus and dental alveoli after tooth extraction STEIGER WHITE and KRIVIT (162) and BARKHAN (24) reported a good haemostatic effect of E ACA in the treatment of haematuria in 3 and 1 patients, respectively, with haemophilia Later, STARK et al (161) felt that E-ACA was a cause of intrarenal obstruction in haematuria of haemophiliacs We have used E-ACA for treatment of haematuria in 6 patients with haemophilia, but we have seen no such side effects REID et al (140) stressed that it is possible to extract teeth in haemophiliacs under protection of E-ACA alone Such treatment is in our opinion, attended by an undue risk of bleeding On the other hand we feel that in coagulopathies conventional substitution therapy should be extended to include E ACA in association with extraction of teeth, for, as already pointed out, it has been shown that in these cases the fibrinolytic activity in the alveoli can increase 3 to 4 days after the extraction (31) GORDON et al (64) have recently published a clinical trial of E-ACA in 10 patients with severe haemophilia during a six week period They expressed the view that the drug may be of prophylactic value in the clinical management of severe haemophilia

Several authors have reported that the presence of fibrinolysis may complicate the bleeding tendency in *leukaemia* (30 a, 39 54 62 78 and others) Fibrinolytic bleedings have been found to be especially common in acute leukaemia of the promyelocyt type (30 a, 125) Judging from our experience in 7 patients with leukaemia and increased fibrinolysis, E-ACA can be recommended as an effective haemostatic agent in cases with leukaemia and enhanced fibrinolytic activity BAKER et al (23) reported a case of acute myelogenous leukaemia with a haemorrhagic syndrome characterized by hypofibrinogenaemia, thrombocytopenia and factor V deficiency In this case E-ACA was reported to have no effect, and it was thought that the bleeding in this patient might have been due to diffuse intravascular coagulation The autopsy findings in our patients revealed no evidence of a defibrination syndrome primarily or as a consequence of the E ACA treatment Several of our patients received large total doses of E-ACA up to as much as 1440 g

Fibrinolysis has also been described as a complication of polycythaemia (30 b) but also in this disease some authors (59) have supposed that the increased fibrinolytic activity is secondary to hypercoagulability and recommended that bleeding should be treated with heparin We have so far treated only one patient with E-ACA because of polycythaemia complicated by fibrinolysis In that case the bleeding stopped after E-ACA and no complications were seen

Miscellaneous diseases An increased fibrinolytic activity is a common finding in *liver disease* especially in liver cirrhosis (21 25 41 43 51 52, 81, 113) It is also known that patients with liver cirrhosis respond with higher fibrinolytic activity than normal persons to certain stimuli, such as electroshock and nicotinic acid (56, 169) The cause of this increased tendency to fibrinolysis in liver cirrhosis is obscure FLETCHER *et al* (56 57) believe that it is due to a failure of the hepatic

clearance mechanism of plasminogen activators ASTRUP et al (22) believe that it is the abundance of portal tissue that is responsible for the tendency to fibrinolysis in these patients We recommend the use of E-ACA in fibrinolytic bleeding complications in liver cirrhosis, spontaneous or in association with surgical procedures In the patients we treated the fibrinolytic activity was suppressed, and the bleedings stopped or decreased Some patients received large total doses, up to 753 g, without any side effects GROSSI, MORENO and ROUSSELOT (68) have studied the effect of E-ACA in 15 cases of liver cirrhosis and found it to inhibit the fibrinolysis without producing side effects LEWIS and DOYLE (88) administered E-ACA to 25 patients with liver cirrhosis without subsequent toxic manifestations ARON et al (21) reported one case of liver cirrhosis in which E-ACA had a definite effect on the bleeding MARCHAL et al (94) treated cases with liver cirrhosis and fibrinolysis with E-ACA and described the results as excellent

Some authors (75, 174) have suggested that the haemorrhagic diathesis in liver disorders is primarily initiated by intravascular coagulation They recommend the use of heparin for treatment of bleedings in such patients NILEHN and NILSSON (115) found no signs of an intravascular coagulation in their investigations of liver disorders, including immunological determination of split products

The cause of bleeding in *chronic ulcerative colitis* is unknown In our patients with this disease the fibrinolytic activity was not increased but the bleeding was nevertheless controlled by E-ACA This may indicate that such bleedings are caused at least in part, by a local release of a plasminogen activator The favourable effect of E ACA on recurrent gastric bleeding (49, 128) may possibly also be explained by a similar local inhibition of fibrinolysis

Induced fibrinolytic states and allergic disorders Like many other authors (28, 47, 53, 106, 131, 156, and others), we recommend the use of E-ACA as an antidote to thrombolytic therapy Thus if a patient undergoing thrombolytic therapy develops haemorrhage, E-ACA should be given intravenously in total doses of at least 10 g—20 g As mentioned above, in one series of patients we gave combined infusions of large doses of SK and E-ACA The purpose was to find out whether E-ACA could inhibit the fibrinogenolytic process in the plasma leading to a haemorrhagic defect without simultaneously inhibiting the thrombolytic process, for, unlike activators, E-ACA is not adsorbed to the fibrin clot (1) It is not yet possible to say anything about the therapeutic effect of combined administration of SK and E ACA, which can therefore not yet be recommended McNICOL et al (101) have studied thrombolysis in an artificial circulation, and they believe that it is highly probable that E-ACA given with SK would inhibit thrombolytic activity *in vivo*

As already pointed out in the introduction, Japanese workers have reported that E-ACA can prevent allergic reactions and that it is effective in the treatment of various diseases of allergic origin Also other authors (76, 171, 176) have found that systemic anaphylaxis in animals such as mice, rats and rabbits is inhibited by injection of E-ACA SPINK and VICK (159) and NEUBAUER (112) reported that lethal doses of endotoxin failed to produce shock in dogs pretreated with E-ACA No explanation can be offered for the favourable effect of E ACA on ana-

phylactic and endotoxin shock We studied the effect of E-ACA in anaphylactic shock in one patient known to be hypersensitive to Meprobamate E-ACA inhibited the fibrinolytic activity, which developed in connection with the shock, but it had no effect on the anaphylactic shock We also administered E-ACA to one patient with severe bronchial asthma and to one patient with severe exfoliative dermatitis, but it had no effect on the condition in these cases Japanese workers (108) also reported E-ACA to have an antipyretic effect We have studied the effect of pyrogens given first alone and then together with E ACA in 3 normal subjects but E ACA did not influence the fever reaction the haematological changes or the fibrinolytic activity induced by pyrogens This suggests that the activator activity caused by injection of pyrogens is different from the spontaneous labile activator in blood SHERRY et al (154) observed an inhibition of the fibrinolytic response to Pyrexal by E-ACA in two cases Since the fibrinolytic response to pyrogens shows great individual variations the experiments are difficult to evaluate because the authors did not compare the effect of infusion of pyrogens alone with that of pyrogens together with E-ACA in one and the same subject DEUTSCH and ELSNER (44) reported that the fibrinolysis following injections of pyrogens is caused by the appearance of a stable type activator in addition to a small amount of a labile type activator Furthermore E-ACA did not influence the frequency of fever reactions occurring after streptokinase infusions Thus we have not been able to confirm the findings that E-ACA has an antiallergic or antipyretic effect in human beings It was however, noteworthy that E-ACA had, for some unknown reason a favourable effect on the symptoms in a patient with periodic angioneurotic oedema In this connection it might, however, be mentioned that STACHER (160) and LOWNEY (92) confirmed the finding of ITOGA and YOGO (73) that local injection of E-ACA can inhibit the tuberculin reaction LOWNEY (92) believes that the effect of E-ACA on the tuberculin reactions is due to its whealing ability rather than to its antifibrinolytic or antiproteolytic qualities

SIDE EFFECTS AND CONTRAINDICATIONS

Two pharmaceutical manufacturers (Merck, Sharp & Dohme Research Laboratories and the Cutter Laboratories) have reported E-ACA in large doses to produce subendocardial haemorrhages in dogs and monkeys JOHANSSON and NILSSON (74) found no such changes in their dog experiments Neither have trials on dogs in other laboratories confirmed the occurrence of subendocardial haemorrhages (102) E-ACA is only slightly toxic in mice and rats (103, 104) MELANDER and coworkers also carried out combined two-generation and chronic toxicity studies on rats They gave four groups of rats 0 mg, 500 mg, 2500 mg and 5000 mg per kg bodyweight a day for 3 months This treatment produced no gross lesions or deaths and histological examination postmortem revealed no tissue injuries in the liver, heart, lungs or kidneys A decrease in pregnancy rate and developmental disturbances were found with E-ACA at the lowest dose tested corresponding to a high clinical dose With increasing doses this trend continued and at the highest doses no pregnancy occurred JOHNSON *et al* (76) also reported that E-ACA is teratogenic in animals On the basis of these observations we would therefore stress that the use of E ACA is

contraindicated in the treatment of women in early pregnancy

Fourty six of our patients who died from their disease soon after they had been treated with E ACA were thoroughly autopsied, no subendocardial bleedings were observed and none of the organs showed any signs of toxic effects of the drug

Of our patients, 7 have received more than 1000 g and 3 more than 4000 g E-ACA At examination after treatment the liver function, the NPN and the blood picture were found to be normal *ECG before and after treatment revealed no changes*

Some authors have described E ACA as a potentially dangerous compound, particularly in the presence of an underlying thrombosing state Since E-ACA is an inhibitor of plasminogen activation it is supposed that E-ACA may cause vascular occlusion by inhibiting the lysis of intravascular fibrin (23, 40, 55, 60, 89, 102, 105) But there is so far no evidence at all that E ACA can cause a defibrination syndrome with intravascular coagulation Nor has any coagulation promoting effect of E-ACA been observed *in vitro* (16, 119) No change in the adhesiveness of platelets as measured by Hellem's method (70, 71) after addition of E ACA to the blood in a concentration of 10 mg/ml has been observed (42) Our material included 3 cases with the defibrination syndrome, namely one patient with gastric cancer, one with pancreatic cancer, and one with cancer of the prostate The patient with cancer of the prostate has been described previously by ANDERSSON (12) In all 3 cases signs of intravascular deposition of fibrin were noted before antifibrinolytic treatment was started All 3 died and at autopsy widespread thrombosis and infarctions were found in the internal organs Judging from the histological examination, the formation of the thrombi in the cases with gastric cancer and pancreatic cancer had preceeded the start of treatment with E ACA Besides the case described by ANDERSSON (12), a similar case of prostatic cancer has been described by NAEYE (111) In the patient described by NAEYE, as in the one reported by ANDERSSON, renal function was impaired and bleeding was controlled by the administration of E-ACA, although the further course was complicated by multiple arterial thrombosis Because of the impaired renal function the concentration of E ACA in the plasma was presumably abnormally high for a longer period during administration of the drug It is not known whether this had any effect on the further course of the disease in these two cases In cases, like these, with a defibrination syndrome in association with fibrinolysis, we believe it is justified not only to try to control the fibrinolytic component with E-ACA, but also to treat the other component of the syndrome, namely the increased tendency to coagulation We therefore recommend to treat such cases with both E-ACA and heparin in relatively small doses, *e g* 2500—5000 I U per dose intravenously

Prostatectomy is often complicated by thrombo embolism In various series the frequency of thrombosis has been given as 8 5 % (36) and up to 27 % (65) Of the 50 patients we treated with E ACA after prostatectomy, 9 had evidence of thrombosis or embolism In our control group not receiving E-ACA 5 of 25 patients had postoperative thrombo embolic complications The incidence of thrombo-embolic complications in these two groups was thus almost identical

Otherwise only a few clinical reports on

adverse effects of the substance have been published. NOUR ELDIN and DRAISEY (129) reported a patient with prostatic carcinoma and metastases, in whom necropsy revealed hepatic and cardiac necroses. The patient had received a total dose of 26 g of E-ACA, and had died about one month after treatment with E-ACA. Liver enlargement had been present already before E-ACA therapy was started. These authors considered the possibility of a side effect of E-ACA being responsible for the observed myocardial changes but in this case other possibilities appear at least equally feasible. STOKES et al. (163) reported thrombosis after E-ACA treatment in a case of lymphosarcomatosis. The increased incidence of thrombosis in neoplastic diseases is, however, well known (50). SWEENEY (164) in his survey also concludes that no unequivocal case of thrombosis secondary to E-ACA treatment has been reported.

In our experience E-ACA cannot be regarded as a thrombogenic agent.

Thus, though we noted no serious side-effect of E-ACA, not even when given in very large doses, the frequency of troublesome, though not severe, side-effects was high. Orthostatic symptoms, nausea and diarrhoea were common, especially among patients who received the preparation in a dose of 0.1 g per kg bodyweight to inhibit generalized fibrinolysis. When the patients were treated simultaneously with ergotamin tartrate (1—2 mg daily), the orthostatic symptoms decreased.

E-ACA is evidently indicated in the treatment of a variety of haemorrhagic conditions where fibrinolysis is the cause or a contributory cause of the bleeding. In the 5 years we have used the preparation in more than 700 cases, we have observed no side effects serious enough to contraindicate its use. In many cases treatment was life saving. Since the mortality from general fibrinolysis and bleeding was formerly high, E-ACA must be regarded as a valuable new comer to the therapeutic arsenal.

Summary

Experience in the treatment of 744 patients with E-ACA suggested that the use of the preparation is indicated in the following situations:

1. *Fibrinolytic haemorrhage in association with delivery.* In these situations the dose should be adequate, 0.1 g per kg bodyweight, and it should be injected rapidly. If there is reason to suspect associated intravascular coagulation, combined treatment with E-ACA and heparin is recommended.
2. *Acute systemic fibrinolysis in association with surgery.* It is mainly major operations on the thorax, pancreas, prostate, liver and genital organs that are complicated by fibrinolysis, but fibrinolytic bleedings can occur after any operation.
3. *Acute systemic fibrinolysis in patients with cancer,* particularly cancer of the prostate and pancreas.
4. Systemic fibrinolytic states complicating various disorders, especially *leukaemia, liver cirrhosis* and Boeck's sarcoid.
5. *As an antidote in thrombolytic therapy.*
6. *Local fibrinolytic activity in the urinary tract* in the following situations:
   a) *After prostatectomy.* E-ACA will substantially reduce blood losses following prostatectomy, especially if the treatment is continued until the urine has become macroscopically clear. Since such treatment allows simultaneous anticoagulation treatment, it is possible to reduce also another considerable risk of operations on the prostatic gland, namely thrombosis and pulmonary embolism.
   b) *Haematuria* in prostatic cancer, prostatic hyperplasia, prolonged haematuria after traumatic injury of the kidney, haematuria in haemophilia and other coagulation defects, and so called essential haematuria.
7. *Ulcerative colitis.*

Dosage of E-ACA. The drug is equally effective whether given orally or intravenously. An effective level of inhibitory activity in the blood requires relatively large doses of E-ACA. In states with increased systemic fibrinolytic activity a dose of 0.1 g per kg bodyweight every 4—5 hours is recommended. For inhibition of local fibrinolytic activity in the urinary tract, a dose of 3 g three times a day has proved sufficient.

The side effects consisted of dizziness, nausea and diarrhoea. No toxic effects of the drug on E.C.G., blood picture, N.P.N. and liver function tests were observed, not even in cases receiving more than 1000 g of E-ACA. Nor did postmortem examination in 46 cases reveal any signs of a toxic effect. No signs of intravascular coagulation in connection with E-ACA therapy

were observed The incidence of thrombo-embolic complications after prostatectomy in patients treated with E-ACA and a series of controls was identical Judging from our experience in this material E-ACA did not act as an agent inducing thrombosis

E ACA is recommended as a useful fibrinolytic inhibitor in bleeding episodes caused by fibrinolysis No side-effects serious enough to contraindicate treatment with E-ACA have so far been seen Treatment with E-ACA has often been life-saving

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From the Department of Medicine (A) and the Department of Clinical Physiology, Lasarettet, Lund, Sweden

Exercise Tests in Male Diabetics

I Electrocardiographic Study

by

TORD KARLEFORS

It is well known that patients with diabetes mellitus commonly have various abnormalities in their vascular system the coronary arteries included [for references see e g Joslin et al (14) and Ellenberg and Rifkin (9)] Liebow and Hellerstein (19) reviewed the cardiac complications of diabetes mellitus From post mortem studies it was evident that there was a greater incidence of coronary arteriosclerosis in diabetics than in non diabetics Electrocardiographic changes in diabetic patients are also known Thus, Lepeschkin (18), reviewing the literature, mentions that the electrocardiogram is pathological in 20—75 per cent of adult diabetics and if the resting ECG is normal, S T changes may be provoked by physical strain In later years other ECG investigations in diabetics have been published Kalliomaki et al (15) found the resting ECG to be essentially normal in 200 diabetics aged 10—64 years, without symptoms and signs of heart disease Only the standard limb leads were taken into consideration Sonnino et al (33) found pathological ECGs in 35 per cent of diabetic patients aged 40—59 years with less than 12 years duration of disease, and in 71 per cent of the diabetics with more than 12 years duration

In preliminary studies the present author observed that in exercise tests male diabetics differed from non-diabetic subjects of corresponding age and sex both as regards the ECG changes and the behaviour of the systolic blood pressure It was therefore decided to undertake a systematic investigation regarding some circulatory parameters in a series of male diabetic patients

In this paper the diabetic patients and control subjects are presented together with some of the methods and the results of the interpretation of the exercise electrocardiograms In following papers (16, 17) other circulatory investigations are reported and discussed

MATERIAL

Diabetic subjects

The series of diabetic patients consisted of 84 males aged 17—44 years Table I shows some clinical data at the examination The dura

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Table I (continued)

Case No	Age (years)	Height (~)	Weight (kg)	Duration of disease (years)	Insulin requirement (I U/day)	Retinopathy	Neuropathy	Nephropathy	ECG code ST/T (IV/V) rest	ECG code ST/T (IV/V) 4 min after work
84	42	166	56 0	9	44	++	0	0	0/0	0/0
31	23	168	61 5	10	40	+++	0	0	0/0	6/0
2	27	169	58 7	10	68	++	+	0	0/0	0/0
49	31	170	73 0	10	0	+	0	0	0/0	6/0
26	35	174	66 5	10	44	+	0	0	0/0	6/0
69	37	178	85 5	10	64	0	0	0	0/0	4/0
17	44	183	77 6	11	48	+	+	0	0/0	4/3
14	19	187	72 5	12	46	+	0	0	0/0	0/0
61	25	181	70 0	12	58	++	+	0	0/0	6/0
11	35	187	81 5	12	48	0	0	0	0/0	6/0
33	34	189	63 5	13	44	+	0	0	0/0	4/3
30	19	174	60 4	14	84	++	0	0	—	—
50	34	171	65 8	14	76	++	+	0	0/0	2/2
59	25	168	63 6	15	46	++	0	0	0/0	4/3
27	42	180	74 0	15	48	++	+	0	7/0	0/0
74	26	169	62 0	16	54	0	+	0	0/0	6/[illegible]
79	40	184	—	16	40	+	+	0	0/0	4/3
85	19	166	59 0	17	80	++	0	0	0/0	4/3
66	22	171	60 1	17	56	+	0	0	0/0	0/0
39	34	176	61 0	17	40	+++	+	+	0/0	3/3
36	41	173	80 5	17	56	+	0	0	0/0	0/0
16	43	180	84 9	17	42	++	0	0	0/0	6/0
15	44	175	76 4	17	40	++	0	0	0/0	4/0
43	25	160	51 0	18	36	++	0	0	0/0	5/3
4	28	174	82 0	18	40	++	0	0	0/0	0/0
38	37	175	62 4	18	52	+	0	0	0/0	0/0
64	24	175	70 2	19	102	+	—	0	7/0	0/0
87	30	176	60 0	19	64	++	0	0	WPW*	—
32	33	174	67 7	19	60	++	0	0	0/0	4/0
25	[illegible]	173	64 6	19	36	++	+	0	0/0	[illegible]/0
37	34	185	79 1	20	40	+++	+	+	7/0	6/0
80	43	169	71 5	21	32	+	0	0	0/0	6/0
13	29	167	58 0	22	52	+++	0	0	0/0	0/0
24	43	175	76 0	22	40	++	+	+	0/0	0/0
19	28	161	61 4	24	34	++	0	+	6/3	3/3
47	28	161	55 0	25	40	+++	+	+	0/0	4/3
[illegible]	34	176	77 6	28	44	++	0	0	0/0	0/0
18	40	173	74 0	28	44	+++	+	+	0/0	4/0
81	43	162	67 0	33	104	+++	0	+	4/0	4/3

*) Wolff Parkinson White syndrome

tion of diabetes for a patient was defined as the time from the earliest definite symptoms, e g polydipsia polyuria diabetic coma to the time of the present examination The duration of disease was relatively easy to determine from available records.

All patients were kept on a regulated diet allowing only restricted amounts of carbohydrate and fat Seventy four patients were treated with insulin, eight (cases 21 28 29 53 60 63 65 and 67) had only dietary restrictions and two (cases 49 and 77) had both these

Table 1

Diabetic subjects Clinical data at the examination and ECG code for S—T segments and T-waves at rest before exercise and 4 min after work
For explanation of symbols and ECG code, see text

Case No	Age (years)	Height (cm)	Weight (kg)	Duration of disease (years)	Insulin requirement (I U/day)	Retinopathy	Neuropathy	Nephropathy	ECG code ST/T (IV/V)	
									rest	4 min after work
72	12	176	52 2	< 1	48	0	0	0	0/0	0/3
75	17	179	52 0	< 1	48	0	0	[illegible]	0/0	6/0
55	21	173	62 0	< 1	28	0	0	[illegible]	0/0	0/0
28	24	174	59 0	< 1	0	0	[illegible]	[illegible]	0/0	0/0
40	25	174	53 7	< 1	24	0	[illegible]	0	7/0	4/0
63	27	172	69 0	< 1	[illegible]	0	0	0	7/0	0/0
42	32	181	80 0	< 1	16	0	[illegible]	0	0/0	0/0
60	32	178	78 1	< 1	0	0	[illegible]	[illegible]	7/0	2/3
48	34	179	67 5	< 1	28	0	0	[illegible]	0/0	4/3
77	37	179	79 5	< 1	0	0	0	[illegible]	6/0	6/0
78	37	181	79 6	< 1	40	0	0	0	0/0	0/0
29	41	182	61 2	< 1	0	0	0	0	0/0	4/0
46	20	182	67 9	1	28	0	0	0	0/0	0/0
53	23	178	65 2	1	0	0	0	0	0/0	4/0
57	28	176	81 3	1	40	0	0	0	7/0	0/0
67	38	176	69 2	1	0	0	0	0	0/0	0/0
70	18	178	63 0	2	36	0	0	0	0/0	0/0
[illegible]	27	172	59 0	2	20	0	0	0	4/0	1/0
21	42	168	71 5	2	0	++	+	0	0/0	0/0
23	26	168	67 0	3	32	0	0	0	0/0	0/0
41	28	183	71 5	3	28	0	[illegible]	0	0/0	0/0
45	32	164	52 4	3	60	0	0	0	0/0	0/3
76	19	178	66 1	4	36	0	0	0	0/0	0/0
8	26	183	73 0	4	28	0	0	0	0/0	6/0
65	35	176	64 9	4	0	0	0	0	6/0	6/0
83	37	163	63 0	4	50	0	0	0	—	—
10	24	186	70 0	5	36	0	0	0	7/0	0/0
44	31	178	81 3	5	40	0	0	0	0/0	4/3
68	40	181	69 0	5	32	+	0	0	0/0	0/0
1	18	173	62 0	6	60	+	0	[illegible]	0/0	0/0
6	22	168	61 5	6	88	0	0	[illegible]	0/0	6/0
71	23	176	57 6	6	36	+	0	0	0/0	0/3
82	24	179	63 0	6	108	0	0	0	7/0	6/0
35	27	171	64 0	6	44	0	0	0	0/0	6/0
52	29	167	68 2	6	40	0	0	0	0/0	6/0
62	36	175	60 0	6	24	0	0	0	0/0	6/0
9	42	176	80 0	6	52	0	[illegible]	[illegible]	0/0	0/0
5	25	169	63 5	7	32	[illegible]	[illegible]	0	0/0	0/0
22	32	179	83 5	7	60	+	0	+	0/0	0/0
3	34	174	72 0	7	24	0	[illegible]	0	0/0	0/0
7	41	176	—	7	28	0	0	[illegible]	0/0	4/0
56	26	166	60 0	8	64	++	0	[illegible]	0/0	5/0
88	27	182	70 0	8	36	+	0	0	0/0	0/0
20	39	172	77 1	8	40	0	0	0	0/0	6/0
54	25	175	77 4	9	64	0	0			

Table I (continued)

Case No	Age (years)	Height (cm)	Weight (kg)	Duration of disease (years)	Insulin requirement (I U/day)	Retinopathy	Neuropathy	Nephropathy	ECG code ST/T (IV/V) rest	ECG code ST/T (IV/V) 4 min after work
84	42	166	56 0	9	44	++	0	0	0/0	0/0
31	23	168	61 5	10	4[illegible]	+++	0	0	0/0	6/0
2	27	169	58 7	10	68	++	+	0	0/0	0/0
49	31	170	73 0	10	0	+	0	0	0/0	6/0
26	35	174	66 5	10	44	+	0	0	0/0	6/0
69	37	178	85 5	10	64	0	0	0	0/0	4/0
17	44	183	77 6	11	48	+	+	0	0/0	4/3
14	19	187	72 5	12	46	+	0	0	0/0	0/0
61	25	181	70 0	12	58	++	+	0	0/0	6/0
11	35	187	81 5	12	48	0	0	0	0/0	6/0
33	34	189	68 5	13	44	+	0	0	0/0	4/3
30	19	174	60 4	14	84	++	0	0	—	—
50	34	171	65 8	14	76	++	+	0	0/0	2/2
59	25	168	63 6	15	46	++	0	0	0/0	4/3
77	42	180	74 0	15	48	++	+	0	7/0	0/0
74	26	169	62 0	16	54	0	+	0	0/0	6/0
79	40	184	—	16	40	+	+	0	0/0	4/3
85	19	166	59 0	17	80	++	0	0	0/0	4/3
66	22	171	60 1	17	56	+	0	0	0/0	0/0
39	34	176	61 0	17	40	+++	+	+	0/0	3/3
36	41	173	80 5	17	56	+	0	0	0/0	0/0
16	43	180	84 9	17	42	++	0	0	0/0	6/0
15	44	175	76 4	17	40	++	0	0	0/0	4/0
43	25	160	51 0	18	36	++	0	0	0/0	5/3
4	28	174	82 0	18	40	++	0	0	0/0	0/0
38	37	175	62 4	18	52	+	0	0	0/0	0/0
64	24	175	70 2	19	102	+	—	0	7/0	0/0
87	30	176	60 0	19	64	++	0	0	WPW*	—
32	33	174	67 7	19	60	++	0	0	0/0	4/0
25	[illegible]	173	64 6	19	36	++	+	0	0/0	6/0
37	34	185	79 1	20	40	+++	+	+	7/0	6/0
80	23	169	71 5	21	32	+	0	0	0/0	[illegible]/0
13	29	167	58 0	22	[illegible]	+++	0	0	0/0	0/0
24	43	175	76 0	22	40	++	+	+	0/0	0/0
19	28	161	61 4	24	34	++	0	+	6/3	3/3
47	23	161	55 0	25	40	+++	+	+	0/0	4/3
12	34	176	77 6	28	44	++	0	0	0/0	0/0
18	40	173	74 0	28	44	+++	+	+	0/0	4/3
81	43	162	67 0	33	104	+++	0	+	4/0	4/3

*) Wolff Parkinson White yndrome

tion of diabetes for a patient was defined as the time from the earliest definite symptoms e g polydipsia polyuria diabetic coma to the time of the present examination The duration of disease was relatively easy to determine from available records.

All patients were kept on a regula ed diet allowing only restricted amounts of carbohydra e and fat Seventy four patients were treated with insulin eight (cases 21 28 29 53 60 63 65 and 67) had only dietary restrictions and two (cases 49 and 77) had both these

and treatment with tolbutamid. Case 63 was given a dosage of 28 units per 24 hours at the time of discharge from the hospital.

All patients have been treated at the Department of Medicine (A). The principal aim has been to try to keep the patient free from glycosuria, and since 1956 they have been taught to make their own urinary tests. Furthermore, they have been seen by a doctor at three monthly intervals. Thus there is reason to assume that the majority of patients have been well regulated. Of course there have to be some exceptions and, judging from available records, glycosuria has been present more often in cases 37, 44, 64, 70 and 79. Cases 27, 30, 45 and 61 have been relatively difficult to regulate and have at times shown rather pronounced variations in blood glucose. A tendency to keto-acidosis has been present in cases 18, 31, 47, 50, 56 and 66.

The diabetic patients had varying occupations and within them were represented all degrees of physical activity. All cases were fully active except patient No. 18 who has a sick pension on account of near blindness.

Retinopathy. Almost all patients have been examined by an eye specialist on one or more occasions with regard to changes in the fundus of the eye. In addition the eyegrounds were inspected at practically all regular check-ups at the Medical clinic.

Retinal changes which are considered to be associated with diabetes mellitus are dilatation and tortuosity of the veins, microaneurysms, haemorrhages, exsudates and the formation of new vessels (2).

In an effort to divide the patients according to the degree of retinal vascular change the following grouping was used. The presence of microaneurysms, haemorrhages, exsudates and formation of new vessels was taken into account. The last mentioned change is considered the most severe form of retinal vascular manifestation of diabetes mellitus.

Degrees of retinopathy have been assessed as follows:

0 this refers to an eyeground without any change of the type associated with diabetes mellitus.

\+ this refers to a mild form of retinopathy with one or two microaneurysms and/or minor haemorrhages.

++ this refers to a moderately severe form of retinopathy with microaneurysms and/or haemorrhages and/or exsudates of greater extent.

+++ this refers to a severe proliferative form of retinopathy with new formed vessels.

The patients were grouped according to the condition observed at the time of examination or shortly before. If the eyegrounds were regarded as entirely normal at the time of examination but had earlier shown a mild degree of retinopathy (+) the patient was still placed in retinopathy group +. As might be expected, most patients without retinopathy had a duration of the disease of less than 5 years and those with a moderate or severe form of retinopathy (++ or +++) had a disease duration of 15 or more years (Table III).

Neuropathy. Information about the presence of neuropathy was obtained from available records. No attempt was made to evaluate the degree of neuropathy. Table I shows the entire case material and the symbol + for neuropathy indicates only the presence of definite subjective and/or objective signs of the condition. Such signs were paresthesia, disturbances of the tendon reflexes and reduced sense of vibration. If the information or the results of examination were dubious or normal in these respects the patient was assigned to neuropathy group 0. From Table I it may be seen that in this case material isolated neuropathy was present in only one patient (case 74), whereas others had neuropathy combined with various degrees of retinopathy. In case 64 the information was not sufficient for the evaluation of neuropathy. In this way the frequency of neuropathy in the group with 0—4 years duration of disease was 4 per cent, in the group with 5—14 years 13 per cent and in the group with 15 or more years 36 per cent. These frequencies are lower than those reported by Steiness (35), who also gave the results of the series published by Bonkalo (6) and Fagerberg (11

The explanation for this is probably that the present author disregarded doubtful signs of neuropathy though a closer examination with special regard to neuropathy could have revealed such a condition. Therefore, in the present investigation the relationship between neuropathy and the circulatory observations was not studied.

Nephropathy. A special examination of renal function was not made. Patients who had a relatively constant albuminuria (cases 18, 19 and 39) were regarded as having nephropathy. Similarly cases 3, 24, 47 and 81 were also assessed as having a renal disorder.

In Table I presence of nephropathy in this sense is indicated by the symbol + and the absence with the symbol 0. Case 3 was found to have albuminuria and a slight pyuria five months after the present investigation. Urinary culture showed no presence of bacteria. The serum creatinine was 0.7 mg/100 ml. On X-ray examination a small concrement was demonstrated in the lower renal pool on the left side. Case 24 often had albuminuria at examination in the out-patient department and in addition two observations of a raised serum creatinine value (1.4 mg/100 ml) were noted in connection with the present examination. Case 47 also had albuminuria as a rule. About eight months after the present examination he was subjected to an intravenous pyelography without pathological findings. This examination was made in connection with a preoperative evaluation for hypophysectomy. The patient suffered from progressive proliferative retinopathy. Finally case 81 had albuminuria and raised serum creatinine values three months before the present examination and also five months later (2.0 and 2.4 mg/100 ml respectively).

Case 18 had suffered from gangrene on the left foot and had been subjected to amputation of two toes. Case 30 had a systolic murmur in the second intercostal space close to the sternum and in addition an X-ray examination of the heart revealed a suspected right ventricular hypertrophy. This motivated examination at the Department of Cardiology and catheterization of the heart, but no support for the presence of organic heart disease was found. Case 31 had suffered from tuberculosis of the left lung and one year prior to the present examination the upper lobe of the left lung had been removed. At the time of the actual examination he was in good condition and an active amateur sportsman.

The patients were divided into age groups 15—24, 24—34 and 35—44 years, into groups according to duration of disease 0—4, 5—14 and 15 or more years in the following called D1, D2 and D3 respectively and into groups according to the degree of retinopathy: no retinopathy, mild, moderate and severe form of retinopathy.

Tables II and III show the number of patients in the various duration groups in relation to age groups and to retinopathy groups.

Table II

Diabetic subjects. Number of patients in different age groups according to duration of disease.

Age group (years)	Duration of disease (years) 0—4 (D1)	5—14 (D2)	15 or more (D3)	n
15—24	8	8	4	20
25—34	11	14	12	37
35—44	7	10	10	27
total	26	32	26	84

Table III

Diabetic subjects Number of patients in different retinopathy groups according to duration of disease

Retino pathy group	Duration of disease (years) 0—4 (D1)	5—14 (D2)	15 or more (D3)	n
0	25	15	1	41
+	0	10	6	16
++	1	6	13	20
+++	0	1	6	7
total	26	32	26	84

Control subjects

In the Department of Clinical Physiology healthy persons are continuously examined in order to provide various circulatory data which later on can be used for comparison with results obtained in patients These persons have been recruited by personal contacts, by advertising at the blood donor unit of the Hospital the students union and at the employment agency of the city In addition the Institute of Social Medicine at the Hospital selected some control subjects as social twins to male diabetics In this manner male subjects of different ages and with different types of occupation have been examined Excluded as controls were only such persons who had suffered from subjective discomfort possibly due to diseases of the heart or vessels and/or respiratory diseases and those who had been treated in hospital or by a doctor with the suspicion of such disease

In order to obtain the same age distribution as that of the diabetics, only subjects in the age range 17—44 years were used Thus the present control group which will be used for comparison with the different diabetic groups consisted of 76 males Table IV shows age height and weight at the time of examination Table V shows the number of controls in different age groups 15—24, 25—34 and 35—44 years Of the 76 control subjects nine were social twins , one belonging to age group 15—24, three to age group 25—34 and five to age group 35—44 years

Comparability of diabetic group and control group

An important question for the present study is how far the diabetic group and the control group are comparable apart from the presence of diabetes mellitus in the former group From a social and occupational point of view the groups are not fully comparable although, on the other hand it cannot certainly be said that a definite difference as regards distribution of various occupations existed It is extremely difficult to obtain a control group for patients with diabetes mellitus Even if only social twins were studied their motivation for the investigation would not be the same as that of the subjects having the disease

In Table VI values are given for ages in the control and the diabetic groups In addition values are given for duration of disease in the different diabetic groups It is apparent from the table that the mean ages in all the diabetic groups and in the comparable control group were about the same The distribution of ages within the different diabetic groups and in the control group was approximately normal

Table IV
Control subjects Age, height and weight at the examination

Case No	Age (years)	Height (cm)	Weight (kg)	Case No	Age (years)	Height (cm)	Weight (kg)
1	26	176	75.0	43	37	174	70.9
2	35	176	82.5	44	41	173	77.5
3	27	174	74.0	45	30	179	63.5
4	26	185	73.0	46	28	179	79.0
5	25	175	67.5	47	29	183	66.5
6	22	178	63.0	48	36	171	70.8
7	22	193	77.2	49	34	177	73.6
8	27	176	74.3	50	44	179	77.9
9	23	166	61.8	52	43	177	80.0
10	44	179	77.0	53	36	176	95.7
11	34	188	75.0	54	36	174	—
13	27	176	69.0	56	38	180	73.0
14	17	182	75.0	57	40	173	69.0
15	34	182	78.0	58	34	177	61.2
16	33	172	68.0	60	40	168	65.0
17	34	192	86.0	61	33	174	74.8
18	27	185	76.0	62	19	180	58.0
19	33	181	72.0	63	19	172	50.0
[illegible]	32	178	83.0	64	15	169	62.4
21	18	172	62.1	65	17	178	63.0
23	41	183	80.0	66	19	177	65.0
24	33	179	77.5	67	18	182	65.0
26	36	181	74.8	68	17	174	69.0
27	24	179	74.2	69	18	183	75.0
28	32	172	55.5	70	17	179	67.0
29	44	185	75.0	71	19	167	61.0
31	33	187	82.0	72	19	177	72.0
32	32	180	74.0	75	21	186	89.2
33	25	173	70.0	77	31	179	91.7
34	27	170	62.6	80	38	173	65.5
35	40	172	67.4	81	39	171	67.7
36	40	177	69.0	82	38	190	100.0
37	24	175	67.6	[illegible]	43	182	74.0
38	26	174	64.5	84	19	169	58.0
39	42	175	59.4	85	28	171	70.0
40	42	176	85.3	86	27	178	75.0
41	33	180	71.5	87	27	168	—
42	34	174	66.0	88	33	184	113.0

Table VI also gives mean values for height and weight for the control group and for the groups D1 D2 and D3 in the diabetic series It is apparent from the table that the average weight in the combined control group 72.4 kg was slightly higher than the average weight in the groups D1 D2 and D3 Furthermore the average height of the controls 177.4 cm was slightly more than in the diabetic groups It seems rather unlikely however that these small differences have any important bearing on the results to be described later

METHODS

All examinations were carried out in the morning Both control subjects and diabetic patients had their usual breakfast and the diabetics had taken their ordinary insulin dose

Table III

Diabetic subjects Number of patients in different retinopathy groups according to duration of disease

Retinopathy group	Duration of disease (years) 0—4 (D1)	5—14 (D2)	15 or more (D3)	n
0	25	15	1	41
+	0	10	6	16
++	1	6	13	20
+++	0	1	6	7
total	26	32	26	84

Control subjects

In the Department of Clinical Physiology healthy persons are continuously examined in order to provide various circulatory data which later on can be used for comparison with results obtained in patients These persons have been recruited by personal contacts by advertising at the blood donor unit of the Hospital, the students union and at the employment agency of the city In addition, the Institute of Social Medicine at the Hospital selected some control subjects as social twins to male diabetics In this manner male subjects of different ages and with different types of occupation have been examined Excluded as controls were only such persons who had suffered from subjective discomfort possibly due to diseases of the heart or vessels and/or respiratory diseases and those who had been treated in hospital or by a doctor with the suspicion of such disease

In order to obtain the same age distribution as that of the diabetics only subjects in the age range 17—44 years were used Thus the present control group, which will be used for comparison with the different diabetic groups consisted of 76 males Table IV shows age height and weight at the time of examination Table V shows the number of controls in different age groups 15—24 25—34 and 35—44 years Of the 76 control subjects nine were social twins one belonging to age group 15—24 three to age group 25—34 and five to age group 35—44 years

Comparability of diabetic group and control group

An important question for the present study is how far the diabetic group and the control group are comparable apart from the presence of diabetes mellitus in the former group From a social and occupational point of view the groups are not fully comparable although on the other hand it cannot certainly be said that a definite difference as regards distribution of various occupations existed It is extremely difficult to obtain a control group for patients with diabetes mellitus Even if only social twins were studied their motivation for the investigation would not be the same as that of the subjects having the disease

In Table VI values are given for ages in the control and the diabetic groups In addition values are given for duration of disease in the different diabetic groups It is apparent from the table that the mean ages in all the diabetic groups and in the comparable control group were about the same The distribution of ages within the different diabetic groups and in the control group was approximately normal

Table VI

Observations in control subjects grouped according to age and in diabetic subjects grouped according [illegible] duration of disease and to degree of retinopathy *Mean values and standard deviations are given for age*, height and weight, and in the diabetic subjects for duration of disease

		Age (years)			Duration (years)			Height (cm)			Weight (kg)		
		n	Mean	S D	n	Mean	S D	n	Mean	S D	n	Mean	S D
Control subjects	Age group (years)												
	15—24	[illegible]	19.5	2.53				20	176.9	6.70	20	66.8	8.60
	25—34	33	30.1	3.27				33	178.2	5.64	32	73.8	10.30
	35—44	23	39.7	2.70				23	176.7	5.12	22	75.3	9.62
	15—44	76	30.2	8.16				76	177.4	5.76	74	72.4	10.14
Diabetic subjects	D1 (0—4 years)	26	28.6	7.56	26	1.2	1.53	26	175.9	5.49	26	66.5	8.84
	D2 (5—14 years)	32	30.3	7.43	32	8.5	2.74	32	175.6	6.47	31	69.0	8.31
	D3 (15 or more years)	26	32.8	7.70	26	19.9	4.47	26	172.2	6.68	25	68.0	9.21
	Retinopathy group												
	[illegible]	41	29.2	7.07	41	3.8	3.79						
	+	16	30.6	8.48	16	12.3	5.18						
	++	20	32.4	8.31	20	15.9	5.86						
	+++	7	33.0	6.98	7	22.1	7.51						

Table V

Control subjects Number of individuals in different age groups

Age group (years)	*n*
15—24	20
25—34	33
35—44	23
15—44	76

before being examined It was intended to have both control and diabetic subjects under conditions which were closely similar to those *during their daily life* The interval between breakfast and the examination varied from 2—4 hours

Electrocardiography

Electrocardiograms were recorded by a four channel ink-writing Mingograph *type 42 B* (Elema Schonander) At rest in the recumbent position the following leads were recorded *standard leads I—III, augmented unipolar* limb leads (aVR, aVL and aVF) and precordial leads V_1 V_*, V_4, V_5 V_6 V_7 and CR_1 CR CR_4 CR_5 and CR_7 *Before the exercise test the indifferent electrode for precordial* leads was moved to the forehead At rest sitting on the bicycle, and during exercise the following leads were recorded CH CH_4, CH_5 and CH_7 (chest head leads)

Exercise test

The test was carried out by sitting exercise on an electrically braked bicycle ergometer (13) essentially as described by Sjostrand (30 31) and Wahlund (37) After mounting the bicycle *the ECG was recorded at rest* Thereafter exercise was started at a load of 300 kpm/min with determinations of heart rate every other minute When a steady state had been reached the load was increased by 300 kpm/min Exercise was stopped when the subject had reached a steady state with a heart rate about 170 beats/min or before that if excessive tiredness or abnormalities made it impossible to *continue*

ECG interpretation

All the electrocardiograms *with* V *and* CR leads were interpreted by an experienced ECG observer who did not know whether the ECG *belonged to a control or diabetic subject* The tracings, made at rest and immediately, four and ten minutes *after exercise were classified* according to the Minnesota code for resting ECG (3) with the modifications given by Blomqvist and Åstrand (4) and Åstrand (1) Only the *S—T* segments and T-waves were coded, since preliminary interpretation showed that in other respects there were no notable differences between the control subjects and the diabetics The modified code published by Åstrand (1) *has been used as regards the S—T* junction and segment and the T wave

S—T junction and segment (measured from preceding P—R interval at onset of QRS, leads I or II, and precordial leads V_4—V_7 and CR_4—CR_7) (Modification of the original code)

IV 1) S—T—J depression 1 mm or more and S—T segment horizontal or downward sloping

2) S—T—J depression 0 5—0 9 mm and S—T segment horizontal or downward sloping

3) No S—T—J depression as much as 0 5 mm but S—T segment sloping down reaching *0 5 mm or more below P—R baseline*

4) No S—T—J depression as much as 0 5 mm but S—T *segment horizontal* or downward sloping but not reaching 0 5 mm below P—R baseline

5) S—T—J depression 1 mm or more with normal configuration of S—T segment

6) S—T—J depression 0 5—0 9 mm with normal configuration of S—T segment

7) S—T segment elevation 1 0 mm or more *(I II III aVL, aVF, V_5 CR_5 or V_7* CR_7)

T—wave items (when R amplitude = 5 mm or more in aVL, or *QRS mainly upright in* aVF, these leads were also used for interpretation)

V 1) T amplitude = *minus 5 mm or more* (I II V_4—V_7 CR_4—CR_7)

2) T amplitude = minus 1 to 5 mm (I II V_4—V_7 CR_4—CR_7)

Table VI
Observations in control subjects grouped according to age and in diabetic subjects grouped according to duration of disease and to degree of retinopathy. Mean values and standard deviations are given for age, height and weight, and in the diabetic subjects for duration of disease

		Age (years) n	Age (years) Mean	Age (years) S D	Duration (years) n	Duration (years) Mean	Duration (years) S D	Height (cm) n	Height (cm) Mean	Height (cm) S D	Weight (kg) n	Weight (kg) Mean	Weight (kg) S D
Control subjects	Age group (years)												
	15—24	20	19.5	2.33				20	176.9	6.70	20	66.8	8.60
	25—34	33	30.1	3.27				33	178.2	5.64	32	73.8	10.30
	35—44	23	39.7	2.90				23	176.7	5.12	22	75.3	9.62
	15—44	76	30.2	8.16				76	177.4	5.76	74	72.4	10.14
Diabetic subjects	D1 (0—4 years)	26	28.6	7.56	26	1.2	1.53	26	175.9	5.49	26	66.5	8.84
	D2 (5—14 years)	32	30.3	7.43	32	8.5	2.74	32	175.6	6.47	31	69.0	8.31
	D3 (15 or more years)	26	32.8	7.70	26	19.9	4.47	26	172.2	6.68	25	68.0	9.21
	Retinopathy group												
	0	41	29.2	7.07	41	3.8	3.7[illegible]						
	+	16	30.6	8.48	16	12.3	5.18						
	++	20	32.4	8.31	20	15.9	5.86						
	+++	7	33.0	6.98	7	22.1	7.51						

3) T-wave flat or small diphasic, negative phase less than 1 mm (I, II V_4—V, CR_4—CR)

This way of interpreting an ECG does not give information on changes that may occur as regards the T-wave from the resting condition before the exercise test to after, provided of course these are not so marked as to alter the classification On account of that, the amplitudes of the R- and T-waves were measured in precordial lead V_5 and the quotient T/R was formed The level of the P—R segment at the beginning of QRS was taken as the baseline

Excluded were the electrocardiograms in which the left precordial leads did not record left type ventricular potentials That occurred in control subjects Nos 33 and 62 and in diabetic patients Nos 10 and 30 In addition one patient case 87, was excluded because his electrocardiogram showed Wolff Parkinson White syndrome As for the ratio T/R this was only calculated for subjects where adequate recordings were available both at rest before exercise and four minutes after the end of the work Thus, for classification there remained 74 controls and 81 diabetic subjects, and for calculation of the T/R ratio 71 controls and 78 diabetic patients

RESULTS

Coding of the electrocardiogram

In Table I the individual items, (V-leads), are given for the diabetic subjects and in Table VII only for the control subjects in whom the tracings were abnormal four minutes after work Table VIII gives the numbers of individuals with normal (symbol 0) and pathological (symbol +) S—T segments and T-waves before exercise and four minutes after (V-leads) in the combined control group and in the diabetic subjects grouped according to duration of disease and to retinopathy Symbol 0 represents a finding interpreted as not pathological, including code numbers IV 0, 5—6 and 7 and V 0 There is ample evidence that the strictly junctional depressions, code IV 5—6, may be of a functional nature (e g 1, 26) and that they should be distinguished from horizontal, segmental S—T depressions, code IV 1—4, which are considered to be more definitely associated with heart disease Symbol + represents code IV 1—4 and V 1—3

In the resting electrocardiograms of the control group, before exercise, there were no abnormalities Four minutes after exercise horizontal S—T depressions (IV 1—4) and flat or small diphasic T-waves (V 3) were found in a small percentage In this group also it was thus possible, with exercise, to provoke pathological changes Three of the S—T changes were classified as IV 2 (4 per cent) and four as IV 4 The youngest subject with the more

Table VII

Control subjects with pathological S—T (code No IV) and T (code No V) changes 4 min after work Case Nos and ages are given

Code No	Case No	Age (years)
IV 2	47	29
	58	34
	80	38
IV 4	4	26
	18	27
	77	31
	81	32
V 3	46	28
	57	40
	58	34
	80	38

Table VIII

Observations in combined control group and in all diabetic groups Number of individuals with normal (symbol 0) and pathological (symbol +) S—T segments and T-waves at rest before exercise and 4 min after work Figures within brackets represent per cent of total

	n	Rest				4 min after exercise			
		ST		T		ST		T	
		[illegible]	+	0	+	0	+	0	+
Control group	74	74 (100)	0 (0)	74 (100)	[illegible] (0)	67 (91)	7 (9)	70 (95)	4 (5)
D1 (0—4 years)	26	25 (96)	1 (4)	26 (100)	0 (0)	20 (77)	[illegible] (23)	23 (88)	3 (12)
D2 (5—14 years)	30	30 (100)	0 (0)	30 (100)	0 (0)	24 (80)	6 (20)	25 (83)	5 (17)
D3 (15 or more years)	25	24 (96)	1 (4)	24 (96)	1 (4)	15 (60)	10 (40)	17 (68)	8 (32)
Retinopathy group									
[illegible]	40	39 (98)	1 (2)	40 (100)	0 (0)	33 (83)	7 (17)	36 (90)	4 (10)
+	16	16 (100)	0 (0)	16 (100)	0 (0)	12 (75)	4 (25)	12 (75)	4 (25)
++	18	18 (100)	0 (0)	17 (94)	1 (6)	11 (61)	7 (39)	13 (72)	5 (28)
+++	7	6 (86)	1 (14)	7 (100)	0 (0)	3 (43)	4 (57)	4 (57)	3 (43)

marked change (IV 2) was 29 years of age and the oldest 38

During testing conditions before exercise there were no conspicuous differences between the electrocardiograms of the control group and those of the diabetic groups However with increasing duration of disease or degree of retinopathy there were higher frequencies of pathological S—T—T changes in the tracings made four minutes after work, no matter whether V or CR-leads were used

In agreement with previous reports (e g 1 26) the frequency of strictly junctional depressions code IV 5—6, was highest in tracings made *immediately* after work and decreased thereafter Four minutes after exercise the frequency of this change in the control group was 27 per cent (V leads) On comparison with the diabetic groups

3) T- wave flat or small diphasic negative phase less than 1 mm (I II V_4—V_7 CR_4—CR)

This way of interpreting an ECG does not give information on changes that may occur as regards the T-wave from the resting condition before the exercise test to after, provided of course, these are not so marked as to alter the classification On account of that the amplitudes of the R and T-waves were measured in precordial lead V_5 and the quotient T/R was formed The level of the P—R segment at the beginning of QRS was taken as the baseline

Excluded were the electrocardiograms in which the left precordial leads did not record left type ventricular potentials That occurred in control subjects Nos 33 and 62 and in diabetic patients Nos 10 and 30 In addition one patient, case 87 was excluded because his electrocardiogram showed Wolff Parkinson White syndrome As for the ratio T/R this was only calculated for subjects where adequate recordings were available both at rest before exercise and four minutes after the end of the work Thus, for classification there remained 74 controls and 81 diabetic subjects and for calculation of the T/R ratio 71 controls and 78 diabetic patients

RESULTS

Coding of the electrocardiogram

In *Table I* the individual items, (V-leads), are given for the diabetic subjects and in *Table VII* only for the control subjects in whom the tracings were abnormal four minutes after work Table VIII gives the numbers of individuals with normal (symbol 0) and pathological (symbol +) S—T segments and T-waves before exercise and four minutes after (V-leads) in the combined control group and in the diabetic subjects grouped according to duration of disease and to retinopathy Symbol 0 represents a finding interpreted as

Table VII

Control subjects with pathological S—T (code No IV) and T (code No V) changes 4 min after work Case Nos and ages are given

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	80	38
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	18	27
	77	31
	81	39
V 3	46	28
	57	40
	58	34
	80	38

not pathological, including code numbers IV 0, 5—6 and 7 and V 0 There is ample evidence that the strictly junctional depressions, code IV 5—6, may be of a functional nature (e g 1, 26) and that they should be distinguished from horizontal, segmental S—T depressions, code IV 1—4, which are considered to be more definitely associated with heart disease Symbol + represents code IV 1—4 and V 1—3

In the resting electrocardiograms of the control group, before exercise, there were no abnormalities Four minutes after exercise horizontal S—T depressions (IV 1—4) and flat or small diphasic T-waves (V 3) were found in a small percentage In this group also it was thus possible, with exercise, to provoke pathological changes Three of the S—T changes were classified as IV 2 (4 per cent) and four as IV 4 The youngest subject with the more

In Table IX the T/R ratios at rest and four minutes after exercise are given for the combined control group and the diabetic groups At rest before exercise the T/R ratios were about the same in the control group and in the diabetic groups, without significant differences Four minutes after the end of the work the T/R ratio was diminished in all groups, the decrease being larger in the diabetics Thus, group D3 and retinopathy group ++ differed significantly from the control group four minutes after exercise

DISCUSSION

A few control subjects exhibited pathological post exercise tracings Similar results were obtained by Rumball and Acheson for example (26) In the age group 19—44 years 31 out of 502 (6 per cent) healthy R.A.F men had more marked S—T changes (IV 1—3) Åstrand (1) concluded from the literature and her own studies that "the frequency of type IV 1—3 S—T changes should be less than 10 per cent in men below 40 years of age about 15 per cent at 40—50 20 per cent at 55 years and about 35 per cent at 60 years of age The above mentioned figures correspond fairly well with the frequency of type IV 1—3 S—T changes in the present control group, males aged 17—44 years Three out of 74 (4 per cent) showed these changes

In contrast to this, the high percentage of S—T—T changes (IV 1—4 V 1—3) in the post exercise electrocardiograms of the diabetic subjects of corresponding ages stands out There are numerous reports and reviews indicating increased incidence of coronary artery disease in diabetic persons (e g 8, 12, 14, 19, 20 21, 24, 28, 34, 38) It is, therefore, not unreasonable to relate the present findings to coronary atherosclerosis As regards the results in the control group it is known from autopsy (e g 7, 10, 22, 25) that coronary sclerosis without clinical symptoms develops early in life It is possible that ECG changes in connection with exercise tests is a sign of non symptomatic coronary heart disease Thus, the incidence of future coronary heart disease is higher in persons with abnormal exercise ECGs (e g 27) However, the high percentage of abnormal post exercise electrocardiographic S—T—T changes in the diabetics in the present study should not as yet be taken unreservedly as a sign of coronary atherosclerosis It is hoped that a follow-up study of this series, with observations of the development of the ECG changes and a correlation to clinical data, will throw more light on that problem

It is known, however, that in diabetics there are also nonatheromatous, intramural vascular lesions of the heart (5) These may constitute a contributing factor to disturbed myocardial function reflected in the abnormal post exercise tracings

It is not possible to decide whether the abnormalities in the post-exercise electrocardiograms are due to complications of the diabetic state or whether they are an essential part of the disturbance of carbohydrate metabolism

there were no clear-cut differences in this respect

R- and T-amplitudes

For reasons mentioned above the amplitudes of the R- and T-waves in lead V_5 were measured In the control group the mean values for the R-wave and the T-wave were 18 5 and 4 4 mm, respectively, which was in good agreement with the figures given for example by Sodi-Pallares (32) citing Kossman and Johnston, 1935, who reported the "normal" mean values for the corresponding measurements to be 18 8 and 4 5 mm, respectively The R-waves in the diabetic groups were significantly lower, the range for the mean values in groups D1—D3 being 13 5—14 3 mm Also, the mean values for the T-waves, 3 1—3 6 mm, were lower in the diabetic groups Since T- and R-wave amplitudes appear to be related, the ratio T/R could be useful in studying minor divergences between the T-waves at rest before and after exercise A high T/R ratio means that the T-wave is high *in relationship to the R-wave*, and a reduction of T/R in the ECG in the period from before exercise to four minutes after means a flattening of the T-wave, since the R-waves on these two occasions were roughly of the same magnitude within the separate groups

Table IX

Observations in combined control group in all diabetic groups
Mean value and standard error of the mean for T/R ratios at rest before exercise and 4 min after work are given

	n	T/R ratio			
		Rest		4 min after exercise	
		Mean	S E M	Mean	S E M
Control group	71	0 248	0 0114	0 212	0 0111
D1 (0—4 years)	24	0 246	0 0220	0 207	0 0190
D2 (5—14 years)	30	0 261	0 0198	0 193	0 0201
D3 (15 or more years)	24	0 217	0 0218	0 138	0 0180
Retinopathy group					
0	38	0.243	0 0166	0 198	0 0159
+	15	0 279	0 0305	0.211	0 0319
++	18	0 226	0 0269	0 130	0 0165
+++	7	0.206	0 0372	0 151	0 0390

pectively In the group with 5—14 years duration of disease, D2, the figures were 20 per cent and 17 per cent, respectively Finally, the group with 15 or more years of disease, D3, showed 40 per cent abnormal S—T changes and 32 per cent abnormal T-wave changes

With increasing degree of retinopathy there were increasing frequencies of pathological S—T—T changes four minutes after work

The T/R ratio at rest in the diabetic groups did not differ significantly from that in the control group Four minutes after work the T/R ratios in group D3 and retinopathy group ++ were significantly lower than in the control group, indicating T-wave flattening

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Wahlberg (36) found the glucose tolerance to be pathological in 46 per cent of patients with atherosclerotic diseases but without clinical diabetes mellitus The corresponding figure in a control group without atherosclerotic diseases or diabetes was 10 per cent The age distribution in both the atherosclerotic and control groups was comparable Ostrander et al (23) found 87 patients with manifest diabetes in an epidemiologic study of 5140 persons These patients had a higher prevalence of vascular disease than the non-diabetic persons of similar age and sex However, among those with coronary heart disease, cerebral or peripheral vascular disease and hypertension, the proportion with elevated blood glucose levels was significantly greater than among persons in the total examined population

In his monograph, Simonson (29) cites studies where administration of glucose provoked S—T—T changes, especially in patients with coronary heart disease In the present study, neither in control subjects nor in diabetics, was there any relationship between the blood sugar levels before the excercise test and the tracings four minutes after work However, it can still not be excluded that changes in myocardial glucose metabolism may play a rôle, for example by influencing the electrolyte distribution

These control and diabetic subjects have been further investigated as regards systolic blood pressure reaction during muscular work, physical working capacity and haemodynamics, including cardiac output and intra-arterial pressures, at rest and during exercise The results obtained will be described in two following papers

SUMMARY

A series of male diabetics is presented together with control subjects, which are used for comparison Seventy-six healthy males aged 17—44 years, and 84 diabetic males with the same age distribution have been subjected to an ordinary exercise test in the sitting position on an electrically braked bicycle ergometer Electrocardiograms have been recorded with the subject in the supine position before work, during work and again in the supine position immediately, four and ten minutes after work The tracings (V-leads) have been classified according to the "Minnesota code" for resting electrocardiograms, with certain modifications given separately in this paper Changes interpreted as pathological have been specified In addition the T/R ratio has been calculated for the tracings made before work and four minutes after

At rest, there were no pathological changes in the control group The diabetic subjects, grouped according to duration of disease and retinopathy, did not differ significantly during resting conditions from the controls Four minutes after the end of the work there were 9 per cent abnormal S—T changes and 5 per cent T-wave changes in the control group In the diabetic group with 0—4 years duration of disease, D1, the corresponding figures were 23 per cent and 12 per cent, res-

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Exercise Tests in Male Diabetics

II Heart Rate and Systolic Blood Pressure

by

TORD KARLEFORS

Vascular changes of various types are well known in diabetes mellitus, for references see Joslin et al, 1959 (25), Ellenberg and Rifkin 1962 (16) These vascular manifestations have mainly been studied by microscopical observations on material obtained by biopsy or at autopsy (1, 2, 17, 20) and by studies of the peripheral circulation using various methods (22 30 35 36, 47) Particular emphasis has been put on skin blood flow (7, 40) These investigations have revealed, in various vascular beds abnormalities which would lead to an increase in the peripheral vascular resistance A generalized increase in the vascular resistance should lead to an increase in the arterial blood pressure

Blood pressure conditions at rest in adult diabetics have been studied by several workers (e g 19 31 38) Martensson (38) studied 219 patients with long standing diabetes (duration of disease 15—34 years) Hypertension i e a systolic blood pressure over 150 mm Hg and diastolic blood pressure over 90 mm Hg was present in 57 per cent of the subjects

Lundbaek (31) studied 164 diabetics with a duration of disease of 15—25 years and found hypertension, defined as blood pressure at rest over 150 mm Hg systolic and/or 100 mm Hg diastolic, in 48 per cent The incidence increased with increasing age, both for men and women and in all age groups women had the higher incidence High blood pressure was present in 50 per cent of the men and 84 per cent of the women over 50 years of age There was no obvious relation between hypertension and the duration of the disease

Freedman et al (19) examined 1100 diabetics of various ages and concluded that there was no difference in the incidence of hypertension between a diabetic and a non-diabetic population with a similar age (10—69 years) and sex distribution In an older age group (70—79 years) hypertension was more frequent in diabetics

In a group of children and teenagers (8—20 years) Moss (37) found that the systolic blood pressure tends to increase significantly in diabetic children at about 13 years of age However,

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cal exercise test in slightly older subjects Table I shows the age height and weight of these controls at the examination The controls were divided into age groups 15—24, 25—34 35—44 and 45—54 years

Comparability of diabetic group and control group

An important question for the present study is how well the diabetic and control groups compare apart from the presence of diabetes mellitus in the former This question was discussed in the previous paper (27) with particular regard to age height and weight

The assumption that the control group used was adequate is further strengthened by the observation that the results in the controls are closely similar to those in the group of diabetics with a short duration of disease It should also be pointed out that the arterial blood pressure at rest and during exercise in the control series is practically identical with observations made in a mixed group of 57 male patients in the same age range and without diabetes or significant heart or lung disease These subjects were examined with an exercise test on account of subjective discomfort for example palpitations precordial pain extrasystoles

It may thus be concluded that the control and the diabetic groups are comparable for the purposes of the present investigation

METHODS

A description of the procedure of the examination and the exercise test has been given previously (27)

Heart rate

The heart rate was determined at rest by measuring the time taken for 15—20 heart cycles on the electrocardiogram during exercise measurements were made every other minute of the time taken for five heart cycles

During exercise circulatory steady state was considered to exist if the heart rate on a certain work load did not increase more than four beats per minute between two observations with a two minute interval In such a case the exercise load was increased and a new steady state was awaited If a steady state was not present after four minutes of exercise this was continued on the same load with measurements of the heart rate every other minute until a steady state was reached or work had to be stopped

All heart rates were recalculated in a uniform manner some time after the examination This recalculation in some instances revealed that certain steady states defined as above had not existed on a particular work load In such a case the heart rate is missing in the tables, whereas it may be given for a higher work load where the existence of a steady state could be confirmed

Using the approximately linear relationship between heart rate and work load the physical working capacity in kpm/min was determined at heart rates of 130/min and 170/min (PWC 130 and PWC 170) by inter and extrapolation (42) Extrapolation to a heart rate of 170/min was not performed in cases where heart rates did not exceed 130/min Exceptions were made in cases with three observations on a straight line If all heart rates were higher than 130/min the line was not extrapolated "downwards On drawing the individual regression line between heart rate and work load the heart rate at the lowest work load was ignored if it was too high in relation to the heart rates at higher work loads. This was considered to be due to emotional factors (control subjects Nos 17 21 22, 27 and 66 diabetic subjects Nos 5 20 42 and 80)

Measurement of blood pressure

Arterial blood pressure was measured by the indirect auscultatory method using a mercury manometer The external dimensions of the blood pressure cuff were 12×49 cm and the expansible rubber balloon measured 10 5 × 30 cm

Special attention was given to the position of the upper arm in relation to the heart. At rest with the subject lying flat on a couch the middle part of the upper arm and the blood pressure cuff were about 5 cm below

he found no statistically significant connection between blood pressure and duration of diabetes

Against this background and after preliminary observations that the systolic blood pressure of male diabetics increased considerably during physical exercise, it was judged to be of interest to compare systematically the systolic blood pressure during exercise in young male diabetics with that in non-diabetic controls It seemed possible that determination of the arterial blood pressure in a situation where larger demands were put on the circulatory system would reveal pathological changes which were not manifest at rest The present paper deals with indirect, auscultatory measurements of arterial blood pressure during a graded physical exercise test on a bicycle ergometer In addition, information was also obtained about the heart rate and the physical working capacity The electrocardiographic changes have been reported separately in a previous paper (27)

MATERIAL

Diabetic subjects

The group of 84 male diabetic patients used was described in a previous paper (27)

Control subjects

The control group, which was compared directly with a diabetic group, consisted of 76 males previously described (27) in the age range 17—44 years The age distribution corresponded to that of the diabetic patients

In addition a group of ten controls aged 45—54 years is presented, since it was also of interest to study the behaviour of the systolic blood pressure during an ordinary physi

Table 1

Control subjects, aged 45—54 years Individual values, mean values and standard deviations are given for age, height and weight

Case No	Age (years)	Height (cm)	Weight (kg)
12	47	178	70 0
22	49	174	66 6
25	49	176	73 8
30	47	181	85 0
51	48	171	51 4
55	46	—	—
59	45	160	58 5
74	53	178	85 0
78	52	174	70 5
89	48	181	74 9
n	10	9	9
Mean	48 4	174 8	70 6
S D	2 50	6 46	11 04

cal exercise test in slightly older subjects Table I shows the age height and weight of these controls at the examination The controls were divided into age groups 15—24 25—34 35—44 and 45—54 years

Comparability of diabetic group and control group

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The assumption that the control group used was adequate is further strengthened by the observation that the results in the controls are closely similar to those in the group of diabetics with a short duration of disease It should also be pointed out that the arterial blood pressure at rest and during exercise in the control series is practically identical with observations made in a mixed group of 57 male patients in the same age range and without diabetes or significant heart or lung disease These subjects were examined with an exercise test on account of subjective discomfort, for example palpitations precordial pain extrasystoles

It may thus be concluded that the control and the diabetic groups are comparable for the purposes of the present investigation

METHODS

A description of the procedure of the examination and the exercise test has been given previously (27)

Heart rate

The heart rate was determined at rest by measuring the time taken for 15—20 heart cycles on the electrocardiogram during exercise measurements were made every other minute of the time taken for five heart cycles

During exercise circulatory steady state was considered to exist if the heart rate on a certain work load did not increase more than four beats per minute between two observations with a two minute interval In such a case the exercise load was increased and a new steady state was awaited. If a steady state was not present after four minutes of exercise this was continued on the same load with measurements of the heart rate every other minute until a steady state was reached or work had to be stopped

All heart rates were recalculated in a uniform manner some time after the examination This recalculation in some instances revealed that certain steady states defined as above had not existed on a particular work load In such a case the heart rate is missing in the tables whereas it may be given for a higher work load where the existence of a steady state could be confirmed

Using the approximately linear relationship between heart rate and work load, the physical working capacity in kpm/min was determined at heart rates of 130/min and 170/min (PWC 130 and PWC 170) by inter and extrapolation (42) Extrapolation to a heart rate of 170/min was not performed in cases where heart rates did not exceed 130/min Exceptions were made in cases with three observations on a straight line If all heart rates were higher than 130/min the line was not extrapolated downwards On drawing the individual regression line between heart rate and work load the heart rate at the lowest work load was ignored if it was too high in relation to the heart rates at higher work loads This was considered to be due to emotional factors (control subjects Nos 17 21 22 27 and 66 diabetic subjects Nos 5 20 42 and 80)

Measurement of blood pressure

Arterial blood pressure was measured by the indirect auscultatory method using a mercury manometer The external dimensions of the blood pressure cuff were 12 × 49 cm and the expansible rubber balloon measured 10.5 × 30 cm

Special attention was given to the position of the upper arm in relation to the heart At rest with the subject lying flat on a couch the middle part of the upper arm and the blood pressure cuff were about 5 cm below

the sternal angle To obtain a similar point of reference during sitting exercise on the bicycle ergometer, the arm in which the blood pressure was measured was kept relaxed in a slightly flexed position resting against the *arm of the examiner*, in such a manner that the middle part of the upper arm and the cuff were on the level of the sternal insertion of the fourth rib Pressure in the cuff was raised as quickly as possible and the cuff was then deflated rather slowly and with an approximately constant rate The brachial artery in the elbow was used for auscultation and systolic blood pressure was noted when regular sounds were audible The diastolic blood pressure was noted when sounds could no longer be heard In the present series, diastolic blood pressure was quite often not *measurable by the auscultatory method during* exercise i e sounds were often notable down to a pressure of 0 mm Hg and there was no distinct point of 'muffling' of the sounds Therefore values for the diastolic blood pressure during exercise were discarded It has recently been shown (29) that diastolic blood pressure measurements are not reliable during exercise whereas systolic blood pressures can usually be estimated with a degree of accuracy not much less than that during rest During exercise, blood pressure was measured in connection with each recording of an electrocardiogram and heart rate i e every other minute

In the tables the blood pressure values refer to measurements taken at rest and in circulatory steady state during exercise In a few cases pressure values are not given — this means either that the systolic blood pressure was for some reason not recorded on the particular work load or that steady state conditions had not been reached

On the accuracy of indirect measurement of the arterial blood pressure during exercise

It is generally agreed that the indirect auscultatory method gives a reasonably correct value for the arterial blood pressure at rest (8 9 10 11 21 24 39 43 46) There is however some uncertainty, particularly for the diastolic pressure As to measurements of arterial blood pressure during exercise knowledge is rather scarce A comparison between indirect and direct blood pressure measurements during exercise on a tread mill was performed by Henschel et al (23) In eleven young healthy males the arterial pressure was registered through a needle in the radial artery The auscultatory pressure was probably measured in the brachial artery During exercise the systolic blood pressure was underestimated at lower work loads whereas after exercise the values were too high Also the diastolic blood pressure was seriously underestimated with increasing errors at higher work loads The authors concluded that arterial blood pressures cannot be estimated indirectly with any degree of accuracy during muscular exercise

Mastropaolo et al (34) compared the directly measured arterial pressures in two cases with indirect measurements obtained by auscultation and phonoarteriographic recording Their observations showed that the indirect methods were more uncertain during exercise than at rest The most common error was underestimation of the intra arterial pressure, but both methods nevertheless gave reasonable results

In this laboratory arterial blood pressure during exercise has been routinely measured by the indirect method since 1962 The results have been largely similar to those obtained by direct methods at later examinations involving arterial puncture However it was judged necessary to make a comparison of the systolic arterial pressure measured simultaneously by the indirect method, in one arm and directly through a catheter in the other arm (29) In 32 patients with various diseases and six healthy subjects there was a good agreement both at rest and during exercise between the systolic arterial pressure values as measured by the two methods In agreement with Henschel et al (23) the diastolic pressure was seriously underestimated during exercise

In our experience therefore the systolic blood pressure may be measured indirectly during exercise with an error which is not

appreciably larger than that inherent in the method as used under resting conditions except in patients with certain types of organic heart disease (unpublished observations)

Nevertheless it was considered necessary to make a comparison of the indirectly measured and the directly measured arterial blood pressure in diabetic subjects also Such measurements were made in seven of the patients in the present case material (cases Nos 26 27 44 54 [illegible] [illegible] and 83) The results were compared with those obtained in six healthy male volunteers The measurements were performed as described by Karlefors Nilsén and Westling 1966 (29) Fig 1 shows the indirectly measured systolic blood pressure in relation to the directly measured systolic pressure on the horizontal axis The values show a fairly even dispersion around the 45 line of identity with a tendency to auscultatory overestimations at pressures around and above 200 mm Hg One patient with diabetes (case No 27) has been examined twice In this

Fig 1 Comparison of indirectly and directly measured systolic blood pressure at rest (open symbols) and during exercise (filled symbols) Triangles represent diabetics and circles controls. The line of identical value is drawn

patient the arterial blood pressure was measured indirectly in the right arm and directly in the left arm A considerable overestimation of arterial blood pressure with the indirect method occurred in this case This was probably due to a higher blood pressure in the right arm during exercise since even at rest the systolic pressure was about 10 mm Hg higher in this arm

It may however be concluded that it is possible to determine the systolic blood pressure with the indirect method during muscular exercise in male diabetics also

Blood glucose

Samples for blood glucose determinations were taken before the exercise test and as a rule 30 minutes after its end

Blood glucose was determined by the glucose oxidase method (33) In most cases capillary blood was used The analyses were performed at the laboratory of the Diabetes Detection Campaign in Southern Sweden During the course of the present investigation it was found (12) that some glycolysis occurred if the sample was allowed to stand for a few hours at room temperature before being analysed. Some samples in the earlier part of the present series may therefore be 0—30 mg/100 ml too low These uncertain values are specially indicated in the tables with an asterisk In the subsequent part of the study blood samples were stored at $+4^{\circ}$ C (12)

Statistical methods

Conventional statistical methods were used for calculation of the mean value median standard deviation and interquartile range (14) A digital computer was used for the majority of the calculations

The statistical comparison between the control group and the diabetic groups was made using Wilcoxon s T test (45) or Mann Whitney s U test (32) The alternative hypothesis as regards the heart rate at rest has been two-sided and during exercise one sided with the following assumptions within the control subjects younger age groups had higher values than older groups within the

Table II

Observations in individual control subjects Heart rate and indirectly measured systolic blood pressure at rest and at different work loads are given together with indirectly measured diastolic blood pressure at rest In addition blood sugar values before, and 30 minutes after, work are given (see also text as regards the blood sugar values)

HR = heart rate (beats/min)

S = systolic blood pressure (mm Hg)

D = diastolic blood pressure (mm Hg)

* = samples not stored at +4° C

Case No	Rest			Work load (kpm/min) 300		600		900		1200		Blood sugar (mg/100 ml)	
	HR	S	D	HR	S	HR	S	HR	S	HR	S	before	after
1	53	120	80	102	—	132	—	158	190	—	—	—	—
2	74	150	95	104	170	132	195	162	210	—	—	—	—
3	59	120	80	75	120	99	150	130	190	—	—	—	—
4	69	120	80	95	135	120	155	147	160	—	—	108	67
5	61	130	80	83	140	103	—	119	180	—	—	—	—
6	88	125	80	—	—	149	—	177	180	—	—	—	—
7	80	130	75	124	145	148	160	168	170	—	—	99	88
8	94	125	80	109	—	137	—	166	—	184	—	—	—
9	67	120	75	95	130	113	160	138	185	—	—	—	—
10	69	115	85	92	—	127	150	—	—	—	—	—	—
11	73	—	—	103	—	123	—	160	170	—	—	—	—
12	79	120	90	100	—	124	—	—	—	—	—	*68	—
13	40	145	80	71	155	91	—	124	200	152	220	—	—
14	50	130	90	87	—	104	—	125	175	152	—	—	—
15	70	110	65	106	—	123	—	158	—	—	—	—	—
16	64	135	90	—	—	120	175	153	185	170	—	—	—
17	63	135	70	87	140	104	165	130	185	160	190	—	—
18	75	135	85	112	165	134	175	145	195	179	220	—	—
19	60	135	85	98	145	—	—	154	170	193	—	—	—
20	63	135	90	108	145	—	—	168	200	—	—	—	—
21	82	115	75	110	120	113	125	139	135	—	—	—	—
22	72	120	80	96	130	112	160	149	—	—	—	—	—
23	67	130	85	92	145	118	165	145	200	—	—	—	—
24	61	110	70	92	145	108	155	134	175	—	—	—	—
25	67	140	85	94	165	116	195	142	230	—	—	—	—
26	71	120	80	100	145	125	160	147	180	170	195	—	—
27	86	150	70	111	170	130	190	164	195	—	—	—	—
28	72	130	60	82	140	125	—	174	190	—	—	—	—
29	72	115	80	101	—	141	155	—	—	—	—	—	—
30	62	120	90	97	140	110	155	133	170	154	—	—	—
31	70	130	85	103	—	121	—	157	—	—	—	—	—
32	60	135	90	94	140	110	160	144	210	166	255	—	—
33	75	120	75	110	125	135	150	154	160	176	180	—	—
34	81	120	70	129	140	150	150	171	175	—	—	115	79
35	77	120	70	107	160	147	—	175	205	—	—	79	73
36	84	125	80	115	145	143	185	180	185	—	—	—	81
37	68	115	65	119	150	154	165	178	170	—	—	85	104
38	93	140	80	138	140	166	160	189	185	—	—	78	78
39	53	120	70	82	165	111	185	134	210	152	200	—	71
40	64	125	80	88	145	108	160	124	180				

Table II (continued)

Case No	Rest HR	Rest [illegible]	Rest D	300 HR	300 [illegible]	600 HR	600 S	900 HR	900 S	1200 HR	1200 S	Blood sugar (mg/100 ml) before	Blood sugar (mg/100 ml) after
41	86	135	75	112	145	132	160	154	175	180	205	89	72
42	71	120	[illegible]	110	135	128	145	166	160	—	—	81	82
43	64	110	80	84	160	112	175	148	210	—	—	74	59
44	74	120	80	104	140	130	160	146	175	—	—	71	63
45	57	120	70	93	140	133	160	—	—	—	—	90	74
46	92	135	80	104	145	122	165	148	170	—	—	98	80
47	60	130	90	96	140	122	170	165	185	—	—	60	70
48	61	110	[illegible]	84	130	109	150	—	—	—	—	70	70
49	85	145	100	125	170	173	190	—	—	—	—	64	63
50	69	130	80	99	140	116	150	140	175	—	—	85	62
51	81	140	90	125	175	160	195	—	—	—	—	69	80
52	58	135	95	106	160	125	180	164	205	—	—	100	70
53	83	155	90	94	160	114	175	140	190	—	—	71	55
54	77	140	[illegible]	106	155	124	180	148	210	—	—	[illegible]	79
55	78	135	80	99	170	121	190	146	220	—	—	—	—
56	62	140	80	86	135	113	160	134	165	—	—	65	[illegible]
57	80	160	100	116	170	142	185	171	210	—	—	71	70
58	64	140	90	108	165	163	195	—	—	—	—	—	—
59	59	110	80	79	125	99	145	138	190	—	—	86	54
60	70	140	95	101	—	132	—	—	—	—	—	76	84
61	[illegible]	130	80	113	160	149	—	174	210	—	—	—	—
62	99	145	90	134	155	153	165	174	165	—	—	—	—
63	79	120	75	114	145	153	165	185	175	—	—	—	—
64	87	145	90	124	155	149	165	174	165	—	—	—	—
65	77	135	70	101	135	126	150	144	165	164	185	—	—
66	75	130	70	113	150	127	165	147	190	172	215	—	—
67	80	145	80	117	150	131	175	164	185	—	—	—	—
68	75	145	85	110	145	131	165	160	175	—	—	—	—
69	73	145	80	99	—	—	—	162	185	—	—	—	—
70	63	140	80	102	155	118	170	144	180	164	205	—	—
71	82	145	70	128	165	152	185	180	195	—	—	—	—
72	77	145	75	125	165	145	180	173	190	—	—	—	—
74	59	135	90	86	—	107	175	134	215	162	—	—	—
75	91	135	80	112	160	127	175	152	185	—	—	87	75
77	83	140	90	124	160	138	185	—	—	—	—	—	—
78	73	140	90	108	155	142	180	—	—	—	—	90	90
[illegible]	[illegible]	130	90	103	140	—	—	—	—	—	—	70	64
[illegible]	70	160	[illegible]	113	190	145	230	184	250	—	—	120	70
82	76	130	90	94	140	112	160	142	180	—	—	—	—
83	76	130	[illegible]	105	130	127	150	156	170	—	—	—	—
84	70	130	80	—	—	143	180	—	—	—	—	—	—
85	96	115	70	115	130	142	155	170	170	—	—	—	—
86	83	140	[illegible]	119	155	151	180	172	200	—	—	—	—
87	86	150	100	104	160	134	180	158	180	—	—	—	—
88	98	130	90	124	160	138	180	—	—	—	—	—	—
89	83	160	90	108	180	138	275	171	220	—	—	—	—

diabetic subjects groups with longer duration of disease or with increased degree of retinopathy had higher values than groups with shorter duration or without or with milder forms of retinopathy on comparison between the control group and the diabetic groups the latter had higher values than the *former*.

As regards the systolic and diastolic blood pressures the alternative hypothesis has been one sided with the following assumptions

Table III

Observations in individual diabetic subjects Heart rate and indirectly measured systolic blood pressure at rest and at different work loads are given together with indirectly measured diastolic blood pressure at rest In addition blood sugar values before, and 30 minutes, after work are given (see also text as regards the blood sugar values)

HR = heart rate (beats/min)

S = systolic blood pressure (mm Hg)

D = diastolic blood pressure (mm Hg)

* = samples not stored at +4° C

Case No	Rest			Work load (kpm/min) 300		600		900		1200		Blood sugar (mg/100 ml)	
	HR	S	D	HR	S	HR	S	HR	S	HR	S	before	after
1	90	—	—	117	140	150	155	175	—	—	—	*160	*160
2	62	135	95	102	180	158	205	178	220	—	—	*212	*214
3	77	170	115	114	—	161	230	—	—	—	—	*278	*217
4	81	135	80	119	185	145	205	173	235	—	—	—	—
5	76	140	80	110	140	130	160	165	210	—	—	*112	*84
6	79	150	90	114	190	144	190	—	—	—	—	*148	*136
7	87	145	95	106	160	125	160	158	180	—	—	*403	*412
8	84	135	85	105	140	133	170	—	—	—	—	*320	*242
9	57	135	90	81	155	102	190	140	215	—	—	*208	*91
10	87	125	75	106	140	128	160	150	170	170	195	*274	*121
11	79	140	70	100	—	126	—	162	225	—	—	*44	27
12	81	125	90	107	155	—	—	—	—	—	—	*293	*263
13	74	140	90	90	160	114	205	—	—	—	—	*60	*30
14	62	140	75	104	150	120	180	158	220	—	—	*188	*79
15	77	145	95	103	165	118	185	147	195	—	—	—	—
16	87	155	100	140	220	168	270	—	—	—	—	—	—
17	66	125	85	107	130	129	150	—	—	—	—	*252	*262
18	89	180	115	118	175	—	—	—	—	—	—	—	—
19	108	160	110	144	200	175	215	—	—	—	—	—	—
20	81	155	85	113	150	124	180	160	220	—	—	*390	*324
21	74	140	90	115	170	—	—	—	—	—	—	*150	*160
22	64	130	90	96	155	114	160	140	170	—	—	—	—
23	70	135	90	111	165	137	—	170	215	—	—	*120	*100
24	60	190	115	96	215	112	240	—	—	—	—	—	—
25	77	135	90	108	145	—	—	—	—	—	—	*131	—
26	73	135	80	112	165	137	190	175	205	—	—	*326	*255
27	66	145	95	90	185	106	235	134	295	—	—	*154	103
28	61	135	85	96	140	128	155	155	195	—	—	*93	*80
29	58	125	85	93	—	115	150	147	170	—	—	*95	*92
30	104	135	85	130	160	158	210	—	—	—	—	—	—
31	80	130	90	116	155	158	205	—	—	—	—	153	*77
32	72	135	85	111	185	149	220	183	220	—	—	—	—
33	79	125	85	110	145	155	175	180	195	—	—	*175	*146
35	80	135	90	119	170	150	190	178	200	—	—	*73	*26
36	59	135	95	85	160	101	175	119	200	—	—	*151	*90
37	79	170	100	102	205	125	220	146	250	—	—	*49	*44
38	87	140	90	122	150	164	175	—	—	—	—	140	*87
39	80	165	95	134	195	—	—	—	—	—	—	403	*378
40	75	115	70	118	155	169	187	—	—	—	—	*182	117
41	67	125	85	100	155	132	165	—	—	—	—	*179	*170

Table III (continued)

Case No	Rest HR	Rest S	Rest D	300 HR	300 S	600 HR	600 S	900 HR	900 S	1200 HR	1200 [illegible]	Blood sugar (mg/100 ml) before	after
42	70	120	70	102	135	110	145	137	175	168	195	*100	—
43	75	140	105	130	155	—	—	—	—	—	—	—	—
44	55	135	95	92	165	112	180	139	210	175	230	*196	119
45	72	125	85	112	145	148	170	—	—	—	—	367	*348
46	84	120	80	115	135	138	145	162	—	—	—	*213	*168
47	98	145	100	136	185	172	220	—	—	—	—	*24	*20
48	78	130	80	124	150	159	170	185	190	—	—	182	*232
49	73	125	85	102	—	116	140	138	175	—	—	*173	*155
50	56	140	95	98	150	130	195	—	—	—	—	193	*149
52	75	120	80	116	145	154	155	—	—	—	—	56	29
53	57	135	80	100	170	139	180	181	205	—	—	179	157
54	76	140	90	106	160	124	170	148	200	176	215	176	133
55	77	125	70	124	150	160	170	—	—	—	—	253	186
56	73	125	90	105	140	137	155	—	—	—	—	215	162
57	81	130	80	92	150	104	165	118	180	136	205	205	138
58	75	145	80	115	165	150	195	—	—	—	—	80	50
59	97	150	80	128	200	152	230	—	—	—	—	226	227
60	67	130	90	—	—	—	—	160	190	—	—	175	152
61	86	150	90	125	145	155	165	—	—	—	—	155	143
62	82	145	70	104	145	152	185	176	200	—	—	199	145
63	77	145	70	108	145	145	170	164	205	—	—	202	192
[illegible]	64	115	70	94	125	114	145	135	180	170	—	214	189
[illegible]	60	145	80	97	165	124	180	—	—	—	—	151	126
66	83	140	70	111	165	136	205	182	210	—	—	110	41
67	90	125	60	136	155	154	180	—	—	—	—	152	97
[illegible]	66	120	90	93	150	113	185	143	210	—	—	263	138
69	88	185	90	131	230	160	220	—	—	—	—	90	80
70	81	130	80	126	—	153	155	—	—	—	—	—	71
71	87	130	90	118	155	169	165	188	190	—	—	170	120
72	71	105	65	105	145	132	170	170	170	—	—	296	137
74	82	155	90	113	170	128	190	156	220	—	—	230	190
75	89	130	80	128	145	155	155	187	190	—	—	320	300
76	60	120	[illegible]	89	130	116	170	148	195	—	—	200	130
77	89	155	90	130	160	160	175	—	—	—	—	271	210
78	[illegible]	120	80	87	130	115	135	141	170	—	—	200	152
79	78	150	95	110	185	129	215	152	255	—	—	154	155
80	66	—	—	103	140	126	160	176	210	—	—	68	23
81	75	170	100	117	200	149	—	—	—	—	—	—	—
82	92	140	90	125	170	155	195	—	—	—	—	—	—
83	106	150	90	137	170	170	200	—	—	—	—	262	263
84	93	145	100	140	175	—	—	—	—	—	—	225	157
85	79	140	80	146	150	162	170	—	—	—	—	390	302
87	65	120	80	101	150	126	170	162	220	—	—	358	338
88	68	150	90	94	150	111	190	—	—	150	220	190	138

within the control subjects older age groups had higher values than younger within the diabeti subje ts groups with longer duration of d sease or with increased degree of retinopathy had higher values than groups with shorter duration or without or with milder forms of retinopathy on comparison of the control group and the diabetic groups the lat ter had higher values than the former

As regards the physical working capa ity (PWC) the alternative hypothesis within the diabetic groups has been two-sided. On com parison between the control group and the diabetic groups the alternative hypothesis has

been one sided with the assumption that the diabetic groups had lower physical working capacity than the control group

Since there were no great discrepancies between the mean values and the medians only the former are given in the tables

Conventional probability levels of significance have been used and marked in the tables with the following symbols

0 p > 0 05 (not significant)
* 0 01 < p < 0 05 (almost significant)
** 0 001 < p < 0 01 (significant)
*** p < 0 001 (highly significant)
— no test performed

RESULTS

1 Heart rate and arterial blood pressure

All observations of the heart rate and arterial blood pressure, at rest and during exercise, are given in Table II for the controls and in Table III for the diabetic subjects

Table IV

Observations in control subjects grouped according to age and in the combined control group Mean values and standard deviations for heart rate and systolic blood pressure at rest and at different work loads are given together with the same data for diastolic blood pressure at rest

	Age group (years)	n	Heart rate (beats/min)		Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	
			Mean	S D	Mean	S D	Mean	S D
Rest	15—24	20	77	10 83	135	11 23	78	7 16
	25—34	32	73	14 35	130	10 16	80	10 11
	35—44	23	71	8 02	131	15 15	84	7 72
	45—54	10	71	9 11	132	14 57	87	4 74
	15—44	75	74	11 91	132	12 14	81	8 88
300 (kpm/min)	15—24	16	115	10 51	150	13 23		
	25—34	27	104	16 83	146	12 64		
	35—44	20	99	10 60	151	15 46		
	45—54	8	101	13 37	155	21 04		
	15—44	63	105	14 72	149	13 72		
600 (kpm/min)	15—24	17	136	14 43	167	14 80		
	25—34	22	133	19 63	166	14 24		
	35—44	20	124	12 16	171	19 86		
	45—54	9	123	19 78	178	20 63		
	15—44	59	131	16 48	168	16 32		
900 (kpm/min)	15—24	19	160	16 [illegible]	177	14 08		
	25—34	25	155	17 99	183	14 58		
	35—44	18	152	17 01	195	20 90		
	45—54	[illegible]	144	14 10	208	22 75		
	15—44	62	156	17 43	185	17 69		

A Controls
Heart rate at rest and during exercise

A summary of the observations is given in Table IV In addition, values are given for a combined age group, 15—44 years, which will be used later for comparison with the different diabetic groups

Generally speaking, the younger subjects tended to have higher heart rates on a particular work load, but differences were significant only at the lowest work load, 300 kpm/min The higher heart rate in the younger age group may be related to the known fact that the maximal heart rate is higher in younger than in older persons (3 4) However, it has been reported that the heart rate on one and the same work load does not vary much in different age groups (3) This is in conformity with the present results

Systolic blood pressure at rest and during exercise

A summary of the systolic blood pressure values in the different age groups and in the combined age group is given in Table IV and Fig 2

In the combined age group 15—44 years the average systolic blood pressure at rest was 132 mm Hg During exercise it increased successively with increasing work loads the averages being 149 168 and 185 mm Hg

There were no significant differences between the age groups at rest or at the two lowest exercise loads in spite of the fact that the heart rates were slightly different, as mentioned previously Only on the highest work load, 900 kpm/min, did the two older groups, 35—44 and 45—54 years, show a significantly higher systolic blood pressure than the younger groups, in spite of the fact that the heart rate was lower

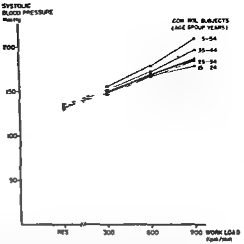

Fig 2 Systolic blood pressure at rest and at various work loads in control subjects grouped *according to age Combined age group 15—44 years* represented by heavy line

The results thus show that an age difference in the systolic blood pressure was only seen at a relatively high exercise load, giving a heart rate of 145—155 per minute

Diastolic blood pressure at rest

A summary of the diastolic blood pressure values at rest within the different age groups is given in Table IV The average value in the combined group

was 81 mm Hg The two older age groups had significantly higher diastolic blood pressures than the youngest group

B Diabetic subjects grouped according to duration of disease Heart rate at rest and during exercise

Table V shows the heart rates in the control group and in the different diabetic groups, D1, D2 and D3, consisting of patients who had been diabetic for 0—4, 5—14 and 15 or more years, respectively

On the whole, the diabetic subjects had slightly higher heart rates than the controls, but the differences were not large At the lowest work load group D3 had a probably significantly higher heart rate than the controls At the work load of 600 kpm/min groups D1 and D2 were also probably significantly different from the control series

Systolic blood pressure at rest and during exercise

The systolic blood pressures in the different groups are shown in Table V and Fig 3 At rest the average systolic blood pressure in the control group was 132 mm Hg and in the three diabetic groups, D1, D2 and D3, 131, 139 and 147 mm Hg, respectively At the lowest work load, 300 kpm/min, the systolic blood pressure had increased to 149 mm Hg in the control series and in the three diabetic groups values of 151, 157 and 174 mm Hg were

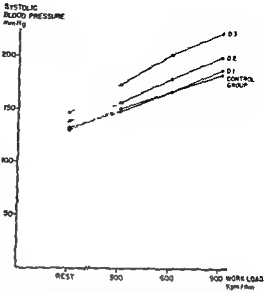

Fig 3 Systolic blood pressure at rest and at various work loads in diabetic subjects grouped according to duration of disease in D1 (0—4 years) D2 (5—14 years) and D3 (15 or more years) and in the combined control group

recorded At 600 kpm/min the corresponding values were for the controls, 168 mm Hg, and in groups D1, D2 and D3, 168, 180 and 203 mm Hg, respectively At the highest work load the systolic arterial pressure averaged 185 mm Hg in the control group and 188, 201 and 224 mm Hg respectively in D1, D2 and D3

A statistical comparison between the control group and the various diabetic groups showed that the difference in systolic blood pressure was highly significant at rest as well as at all exercise levels for the patients in group D3 The difference between the controls and the D2 group was probably significant at rest and at the lowest work load differences at 600 kpm/min and 900 kpm/min were significant and highly significant, respectively There were no significant differences from the con

Table V

Observations in control group and in diabetic subjects grouped according [illegible] duration of disease Mean values, standard deviations and significances for differences from control group for heart rate and systolic blood pressure at rest and at different work loads are given together with the same data for diastolic blood pressure at rest

			Heart rate (beats/min)			Systolic pressure (mm Hg)			Diastolic pressure (mm Hg)		
		n	Mean	S D	Significance for difference from control group	Mean	S D	Significance for difference from control group	Mean	S D	Significance for difference from control group
Rest	Controls	75	74	11 91	—	132	12 14	—	[illegible]	8 88	—
	D1	26	74	11 95	0	131	11 43	0	80	8 12	0
	D2	31	76	11 67	0	139	13 96	*	88	8 84	*
	D3	25	79	11 64	0	147	17 72	**	93	12 00	**
300 kpm/min	Controls	63	105	14 72	—	149	13 72	—			
	D1	23	111	14 51	0	151	12 76	0			
	D2	29	110	13 03	0	157	19 35				
	D3	26	114	17 25		174	24 70				
600 kpm/min	Controls	59	131	16 48	—	168	16 32	—			
	D1	23	140	19 40		168	15 87	0			
	D2	30	138	18 93		180	21 71	*			
	D3	20	136	23 21	0	203	33 97	**			
900 kpm/min	Controls	67	156	17 43	—	185	17 69	—			
	D1	13	159	20 38	0	188	14 77	0			
	D2	18	160	16 46	0	201	17 68	*			
	D3	12	155	20 49	0	224	31 03	*			

trol values in group D1, either at rest or during exercise

A statistical comparison between the different groups of diabetic subjects showed that even at rest the difference between the group with shortest duration and that with the longest duration of disease was highly significant, this did not change during exercise The difference between groups D1 *and D2 was probably significant* at rest and during the two higher work loads, but not at the lowest work load It should be noted that the number of observations in diabetic subjects at the highest work load was smaller than at lower work loads, this was due to the fact that some subjects did not manage the highest work load

To sum up, it may be said that the use of the exercise test made it possible to reveal, more clearly than by observations at rest, an abnormally high *systolic arterial pressure in subjects* who had been diabetic for 5—14 years This abnormal rise of the systolic blood pressure could not be explained by a difference in the heart rate

Diastolic blood pressure at rest

The mean values for diastolic blood pressure in the different groups are shown in Table V The average diastolic blood pressure in the control group was 81 mm Hg In the three diabetic groups D1, D2 and D3 mean values of 80, 88 and 93 mm Hg, respectively were recorded, the two last mentioned values being highly significantly higher than the control value

In spite of the fact that the differences in the diastolic pressure at rest were highly significant, the absolute *values in the diabetic groups were not* so high that any definite abnormality would have been suspected, particularly with regard to the many difficulties inherent in the indirect measurement of diastolic blood pressure

C Diabetic subjects grouped according to retinopathy Heart rate at rest and during exercise

The mean heart rates in the various retinopathy groups 0, +, ++ and +++, *described previously (27),* and in the control group are shown in Table VI

On the whole, there were no clear-cut differences in heart rate between the retinopathy groups and the control group, but the heart rates were slightly higher in the diabetic subjects At the *lowest work load, heart rate in retinopathy group ++* was probably significantly higher than in the control group, and at 600 kpm/min the heart rate was probably significantly higher in the groups 0 and ++ At rest and *during the highest* work load there were no significant differences in heart rate

Systolic blood pressure at rest and during exercise

The average values for the systolic *blood pressure* in the retinopathy groups and in the control group are shown in Table VI and Fig 4

At rest the mean *systolic arterial* pressure in the control group was 132

Table VI

Observations in control group and in diabetic subjects grouped according to degree of retinopathy. Mean values, standard deviations and significances for differences from control group for heart rate and systolic blood pressure at rest and at different work loads are given together with the same data for diastolic blood pressure at rest

		n	Heart rate (beats/min) Mean	SD	Significance for difference from control group	Systolic pressure (mm Hg) Mean	SD	Significance for difference from control group	Diastolic pressure (mm Hg) Mean	SD	Significance for difference from control group
Rest	Controls	75	74	11.91	—	132	12.14	—	81	8.88	—
	0	41	76	11.42	0	136	15.08	0	83	9.88	0
	+	14	72	9.38	0	133	10.51	0	85	8.32	*
	++	20	79	14.11	0	142	15.00	*	93	9.93	***
	+++	7	82	8.51	0	157	18.68	*	99	8.52	**
300 kpm/min	Controls	63	105	14.72	—	149	13.72	—			
	0	36	110	13.92	0	155	18.59	*			
	+	15	105	10.73	0	151	14.[illegible]8	0			
	++	20	117	17.36	*	172	24.07	**			
	+++	7	116	16.33	0	182	19.55	**			
600 kpm/min	Controls	59	131	16.48	—	168	16.32	—			
	0	38	138	18.79	*	174	19.70	0			
	+	16	130	20.17	0	173	21.13	0			
	++	15	143	21.00	*	204	32.18	***			
	+++	4	142	27.26	0	213	8.66	**			
900 kpm/min	Controls	62	156	17.43	—	185	17.69	—			
	0	24	158	16.98	0	196	17.55	*			
	+	12	15[illegible]	22.56	0	202	22.90	*			
	++	6	163	19.09	0	231	33.97	**			
	+++	—	—	—	—	—	—	—			

trol values in group D1, either at rest or during exercise

A statistical comparison between the different groups of diabetic subjects showed that even at rest the difference between the group with shortest duration and that with the longest duration of disease was highly significant, this did not change during exercise The difference between groups D1 and D2 was probably significant at rest and during the two higher work loads, but not at the lowest work load It should be noted that the number of observations in diabetic subjects at the highest work load was smaller than at lower work loads, this was due to the fact that some subjects did not manage the highest work load

To sum up, it may be said that the use of the exercise test made it possible to reveal, more clearly than by observations at rest, an abnormally high systolic arterial pressure in subjects who had been diabetic for 5—14 years This abnormal rise of the systolic blood pressure could not be explained by a difference in the heart rate

Diastolic blood pressure at rest

The mean values for diastolic blood pressure in the different groups are shown in Table V The average diastolic blood pressure in the control group was 81 mm Hg In the three diabetic groups D1, D2 and D3 mean values of 80, 88 and 93 mm Hg, respectively were recorded, the two last mentioned values being highly significantly higher than the control value

In spite of the fact that the differences in the diastolic pressure at rest were highly significant, the absolute values in the diabetic groups were not so high that any definite abnormality would have been suspected, particularly with regard to the many difficulties inherent in the indirect measurement of diastolic blood pressure

C Diabetic subjects grouped according to retinopathy Heart rate at rest and during *exercise*

The mean heart rates in the various retinopathy groups 0, +, ++ and +++, described previously (27), and in the control group are shown in Table VI

On the whole, there were no clear-cut differences in heart rate between the retinopathy groups and the control group, but the heart rates were slightly higher in the diabetic subjects At the lowest work load, heart rate in retinopathy group ++ was probably significantly higher than in the control group, and at 600 kpm/min the heart rate was probably significantly higher in the groups 0 and ++ At rest and during the highest work load there were no significant differences in heart rate

Systolic blood pressure at rest and during exercise

The average values for the systolic blood pressure in the retinopathy groups and in the control group are shown in Table VI and Fig 4

At rest the mean systolic arterial pressure in the control group was 132

'late diabetic complications' at an ordinary clinical examination In these cases, then, the rise in systolic blood pressure during exercise revealed a circulatory abnormality which was not demonstrable by other simple means

Diastolic blood pressure at rest

The mean diastolic blood pressures in the retinopathy groups and in the control group are shown in Table VI In the control group the mean diastolic blood pressure was 81 mm Hg and in the four retinopathy groups, 0 +, ++ +++, it was 83, 85 93 and 99 mm Hg, respectively

The differences between the two most severe retinopathy groups and the control group were highly significant but there was no significant difference between the diabetic group without retinopathy and the control group

It was mentioned previously that this group 0 also had a normal systolic blood pressure at rest However the systolic blood pressure was significantly higher on the highest work load

2 Physical working capacity

The physical working capacity is usually defined as the total oxygen transporting capacity This aerobic capacity can be determined accurately by measurement of the maximal oxygen uptake at a maximal work load For obvious reasons a maximal physical performance cannot be used in clinical practice which means that the maximal oxygen uptake cannot be determined accurately In the present study a very strenuous exercise was definitely contra indicated, since some patients had vascular complications, and since it had been found initially that many patients had pronounced rises in systolic blood pressure during exercise

Since there is an approximately linear relationship between oxygen uptake and heart rate, one can determine the former by extrapolation from values of the heart rate at submaximal work loads, provided that the maximal heart rate is known In this manner the aerobic capacity can be evaluated without determination of the maximal oxygen uptake Since the maximal heart rate decreases with increasing age, corrections must be made so that the lower maximal heart rate of the older subjects does not lead to an overestimation of their aerobic capacity Correction factors for age and nomograms for the determination of the maximal oxygen uptake from the heart rate at submaximal work loads have been published by Åstrand and Ryhming, 1954 (5) and Åstrand 1960 (3) However in the present study these tables could not be used with confidence since it was not certain that the diabetic patients had a normal maximal heart rate

However it was desirable to compare the physical working capacity of controls and diabetic subjects To this end the approximately linear relationship between heart rate and work load was used The physical working capacity (PWC) was given as the calculated work load at two heart rates 130/min and 170/min (PWC 130 and PWC

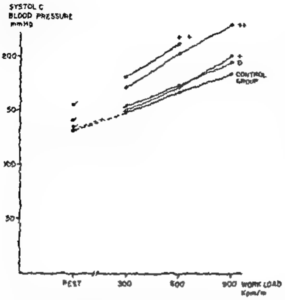

Fig 4 Systolic blood pressure at rest and at various work loads in diabetic subjects grouped according to retinopathy in 0 +, ++ and +++ (see text) and in the combined control group

mm Hg against 136, 133, 142 and 157 mm Hg in the four retinopathy groups 0, +, ++, +++, respectively At 300 kpm/min the systolic blood pressure in the control group averaged 149 mm Hg and in the retinopathy groups, 155, 151, 172 and 182 mm Hg At 600 kpm/min the corresponding values were, for the control group 168 mm Hg, and for the retinopathy groups, 174, 173, 204 and 213 mm Hg On the highest work load, finally, the average systolic blood pressure was 185 mm Hg in the control group and in the retinopathy groups, 0, + and ++, 196, 202 and 231 mm Hg, respectively

A statistical comparison between the control group and the retinopathy groups showed that the systolic blood pressure in those patients with retinopathy graded as ++ and +++ was already significantly higher at rest Highly significant differences were observed at all work loads It should be especially pointed out that at rest there was no significant difference between the control group and the groups without, 0, or with mild, +, retinopathy The differences between these two diabetic groups and the control group were significant at 900 kpm/min, whereas significant differences in heart rate were not present

The observations thus show that with increasing degree of retinopathy there was an increasing tendency to abnormally high systolic blood pressure at rest, and particularly during exercise This was not unexpected since in the present case material the degree of retinopathy increased with the duration of the disease (27) as is generally the case (e g 2, 15) In a previous section it was shown that the arterial blood pressure was higher in groups with longer duration of diabetes

Of particular interest was the finding that the group of diabetic subjects with entirely normal eyegrounds showed abnormally high systolic blood pressures during moderate to heavy physical exercise, in spite of the fact that the systolic blood pressure at rest was not significantly different from that in the controls The patients in this group had no signs of neuropathy or nephropathy, as defined previously (27), with the exception of case No 74, whose tendon reflexes were absent Except for this subject, all patients would have been judged to be without

3 Blood glucose

The individual blood sugar values for the controls and the diabetics are given in Tables II and III, respectively

Blood glucose changes were evaluated only in subjects in which samples were available immediately before the exercise test and 30 minutes after its completion and if the samples had been stored at $+4°$ C The amount of exercise performed was not taken into account Among the diabetics there were 30 subjects fulfilling these criteria They had eaten breakfast as usual and were either insulin treated 25 cases or had dietary restrictions only five cases The patients were compared with 25 control subjects

There was a wide variation in blood glucose in the diabetic subjects An important question in this connection is whether the initial level of the blood glucose was related to the heart rate and the systolic blood pressure during the subsequent exercise test Fig 5 shows the blood sugar value immediately before the exercise test in relation to the heart rate and the systolic blood pressure at 600 kpm/min for diabetics grouped according to duration of disease It is apparent from the figure that there is no relationship between the initial blood glucose level and the circulatory response to exercise Tables II and III show that blood glucose values as a rule decreased during the examination this decrease being more pronounced in the diabetic subjects than in the controls

The average decrease in blood sugar was 11 mg/100 ml for the 25 controls and 50 mg/100 ml for the 25 insulin treated diabetics In five diabetics, treated by dietary restrictions only, the blood sugar dropped an average of 27 mg/100 ml in the corresponding time period

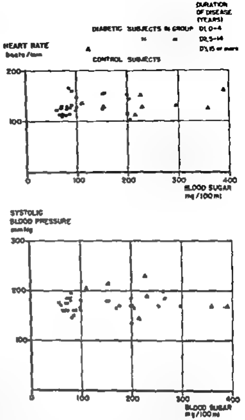

Fig 5 Heart rate and systolic blood pressure at 600 kpm/min in relationship to the blood sugar value before the exercise test, in diabetic subjects grouped according to duration of disease and in control subjects

The blood sugar decrease in connection with the present examination can obviously be due to the muscular work, but a postprandial drop in blood glucose and an effect of the morning insulin dose are probably also important factors

170), for discussion and references see Sjostrand, 1960 (42) The mean values for PWC 130 and PWC 170 for the different age groups in the control material and for the diabetic patients, grouped with regard to duration of disease and retinopathy, are shown in Table VII

All groups, diabetics as well as controls, showed a physical working capacity which was within the expected range, although the diabetic subjects had slightly lower values PWC 130 was probably significantly higher in the control group than in the group D1 PWC 170 was significantly higher in the control group than in the groups D1 and D2 A comparison between the control group and the retinopathy groups showed that the PWC 130 was probably significantly higher in the former group than in the groups without retinopathy, 0, and with retinopathy graded as ++ In addition, PWC 170 was significantly higher among the controls than in the group without retinopathy, 0, and probably significantly higher than in the group ++

Table VII

Observations in control subjects grouped according to age and in the combined control group and in diabetic subjects grouped according to duration of disease and to degree of retinopathy

Mean values, standard deviations and significances for differences from control group for PWC 130 and PWC 170 are given (see text)

		n	PWC 130 Mean	PWC 130 SD	PWC 130 Significance for difference from control group	PWC 170 Mean	PWC 170 SD	PWC 170 Significance for difference from control group
Control subjects	Age group (years)							
	15—24	15	550	164		1042	207	
	25—34	19	600	178		1053	232	
	35—44	18	669	144		1136	209	
	15—44	52	610	167		1079	217	
Diabetic subjects	D1 (0—4 years)	20	545	205	*	953	293	**
	D2 (5—14 years)	28	554	168	0	962	247	**
	D3 (15 or more years)	13	579	163	0	1018	232	0
	Retinopathy group							
	0	34	551	180	*	959	256	**
	+	14	605	177	■	1031	292	0
	++	11	514	178	*	936	220	*
	+++	—	—	—	—	—	—	—

3 Blood glucose

The individual blood sugar values for the controls and the diabetics are given in Tables II and III, respectively

Blood glucose changes were evaluated only in subjects in which samples were available immediately before the exercise test and 30 minutes after its completion and if the samples had been stored at +4° C The amount of exercise performed was not taken into account Among the diabetics there were 30 subjects fulfilling these criteria They had eaten breakfast as usual and were either insulin treated, 25 cases or had dietary restrictions only five cases The patients were compared with 25 control subjects

There was a wide variation in blood glucose in the diabetic subjects An important question in this connection is whether the initial level of the blood glucose was related to the heart rate and the systolic blood pressure during the subsequent exercise test Fig 5 shows the blood sugar value immediately before the exercise test in relation to the heart rate and the systolic blood pressure at 600 kpm/min for diabetics grouped according to duration of disease It is apparent from the figure that there is no relationship between the initial blood glucose level and the circulatory response to exercise Tables II and III show that blood glucose values as a rule decreased during the examination this decrease being more pronounced in the diabetic subjects than in the controls

The average decrease in blood sugar was 11 mg/100 ml for the 25 controls and 50 mg/100 ml for the 25 insulin treated diabetics In five diabetics, treated by dietary restrictions only the blood sugar dropped an average of 27 mg/100 ml in the corresponding time period

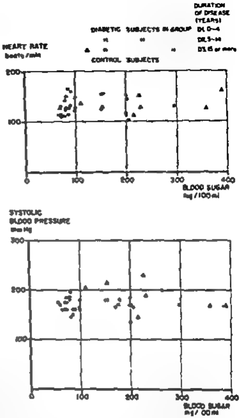

Fig 5 Heart rate and systolic blood pressure at 600 kpm/min in relationship to the blood sugar value before the exercise test in diabetic subjects grouped according to duration of disease and in control subjects

The blood sugar decrease in connection with the present examination can obviously be due to the muscular work, but a postprandial drop in blood glucose and an effect of the morning insulin dose are probably also important factors

DISCUSSION

In comparison with the control material, male patients with a duration of diabetes of five years or more showed an abnormal increase in systolic blood pressure during physical exercise in the sitting position on a bicycle ergometer. A tendency to higher systolic pressures could already be traced at rest, but became much more obvious during exercise. Also, the diastolic blood pressure at rest increased with increasing duration of diabetes. It is of particular interest that the systolic blood pressure during exercise was significantly higher in a group of diabetic subjects which had no "late diabetic complications", and which at rest did not differ significantly from a control group as regards either the systolic or the diastolic blood pressure. It is, of course, not possible to decide whether this group is composed of individuals with a tendency to abnormal blood pressures who developed diabetes, or whether they are primarily diabetics with the abnormal blood pressure as an early sign of vascular complication.

The observed changes in arterial blood pressure in diabetic subjects will now be discussed with consideration of factors such as stroke volume, degree of physical fitness, influence of catecholamines and vascular and renal changes.

A rise of the systolic arterial pressure may be seen under circumstances in which the stroke volume is large and/or the elasticity in the aorta and the big arteries is decreased. Large stroke volumes may be found in well-trained persons. From the results presented it may, however, be seen that the diabetic groups had a somewhat lower physical working capacity than the control group. A larger stroke volume is therefore unlikely. Although statistically significant, the differences in physical working capacity were relatively small and it seems rather unlikely that these differences can be of decisive importance in explaining the differences in the systolic blood pressure during exercise. The relationship between the physical working capacity, i.e. the degree of physical fitness, and the arterial blood pressure is not clear, however. Recent observations (6) have indeed shown that training, with a subsequent increase of the working capacity, leads to an increase of the intra-arterial pressures in a group of young healthy men.

It is well known that tachycardia and a systolic blood pressure rise occur after infusion of adrenaline (e.g. 48), and also that insulin hypoglycaemia leads to a release of catecholamines, particularly adrenaline (e.g. 18, 44). None of the diabetic subjects examined showed any symptoms of hypoglycaemia in close connection with the exercise tests. The question, however, arises whether the rather large decrease in blood sugar in the diabetics treated with insulin may, nevertheless, have caused an increased release of adrenaline. If so, higher heart rates would have been expected in the diabetic subjects. This was not the case. Moreover, there was no relation between the initial blood sugar level and the

haemodynamic response to exercise This question will be further analysed in a following paper (28), in which a more detailed haemodynamic analysis involving intra-arterial pressure measurements and determinations of the cardiac output, is made

In this connection the observation of Barany (7) should be mentioned He found that an intravenous infusion of noradrenaline gave a significantly higher increase in arterial blood pressure in a group of young diabetics than in a control group It has been shown that the noradrenaline level in the plasma rises rapidly with increasing work loads in healthy subjects (13 44) and, in view of this it seems possible that a supersensitivity to noradrenaline plays a role in the abnormal systolic blood pressure rise in the diabetic group It thus seems reasonable to assume that blood pressure conditions in diabetic subjects during exercise may be due to both functional and organic changes in the vessels

Atherosclerotic changes in the larger arteries develop earlier and are more pronounced in diabetic subjects (e g 25) These changes lead to diminishing elasticity of the arterial tree The arterial pulse wave velocity is higher in patients with coronary sclerosis (41) and in diabetic subjects without signs of atherosclerosis or hypertension (47) This has been interpreted as a sign of diffuse atherosclerosis

The form of the arterial pressure curve in the fingers of diabetics has been studied indirectly (30) A diminution or total disappearance, of the dicrotic incisure was found in 62 per cent of young diabetics without clinical signs of vascular complications These findings were thought to be due to reduced elasticity in the larger arteries or to organic changes in smaller peripheral vessels It seems likely that these indirect signs of pathological changes in the larger arteries are relevant to the interpretation of the high systolic blood pressure during exercise in diabetic patients, as observed in the present study

However, the systolic blood pressure rise during exercise can obviously be an early expression of hypertension in the usual sense of the word A renal etiology is possible (25) This assumption is supported by the fact that the diastolic blood pressure was increased at rest in diabetic patients with a duration of disease of five years or more However the increase in systolic blood pressure during exercise would appear to be an earlier sign since it existed in a diabetic group without retinopathy, in spite of the fact that systolic and diastolic pressures at rest did not differ from the control group

The present study thus gives no information about the causes of the blood pressure changes during *exercise in diabetic subjects* although it seems reasonable to assume that the increased systolic blood pressure may be due to at least two different factors The first factor of importance would appear to be a diminished elasticity in the larger arteries possibly of atherosclerotic nature As far as can be seen from the

present study, such changes do not appear until after some years of diabetes. The second factor could be an increased peripheral vascular resistance which would lead to increased diastolic pressure.

It seems possible that studies of the abnormal systolic blood pressure reaction, provoked by physical exercise in certain diabetic patients, may have some prognostic significance. Blood pressure conditions during an exercise test are probably more informative than observations at rest, when evaluating the "stress" to which the system is exposed during daily life. The Framingham study (26) clearly revealed that the morbidity from coronary heart disease was increased in subjects with raised blood pressure. In this respect the systolic blood pressure was of equally good prognostic value as the diastolic blood pressure. In addition, the results of the Framingham study suggested that the risk of developing coronary heart disease was also increased in subjects with a blood pressure which was slightly raised, but not to hypertensive levels. In this connection the results described in the previous paper (27) should be emphasized: there was a high percentage of abnormal electrocardiographic changes after the exercise test in the present case material. These changes may possibly reflect heart disease.

Firm knowledge about the prognostic information given by a simple exercise test in diabetics can, of course, not be obtained until the patients in the present series have been adequately followed up. Whatever the outcome of this may be, the exercise test, as used in the present study, appears to give new information about vascular changes in diabetics. The information is quantitative and can be used for evaluation of the degree of vascular involvement.

Some patients in the present series were also subjected to a more detailed haemodynamic study, in which the results obtained in the simple exercise test as regards arterial blood pressure were confirmed (28).

SUMMARY

A control group of healthy males, 76 aged 17—44 years, and 10 aged 45—54 years, and 84 male diabetic patients aged 17—44 years, have been subjected to an exercise test using submaximal work loads in the sitting position on a bicycle ergometer, with auscultatory measurement of the systolic blood pressure.

In the control subjects the systolic blood pressure during exercise at the highest load was higher in older subjects than in younger ones, without differences in heart rate or systolic blood pressure at rest.

The diabetic subjects were grouped according to duration of the disease and the degree of retinopathy present. There were no differences in arterial blood pressure between the controls and the group of diabetics with 0—4 years disease. In the group with 5—14 years of diabetes, an abnormally high systolic blood pressure could be revealed during exercise more easily than at

rest A group with 15 years or more of diabetes had higher pressures even at rest

In a group of diabetic subjects without retinal changes or other late diabetic complications, according to the criteria used in the present examination it could be shown that the exercise test revealed a circulatory disturbance in the form of an abnormally high systolic blood pressure The blood pressures at rest were normal in this group Another group of diabetic patients, with a mild form of retinopathy (a few microaneurysms and/or haemorrhages), did not differ from the control group as regards the systolic blood pressure at rest whereas during exercise it became abnormally high also In this group the diastolic blood pressure was slightly higher than in the control group at rest Groups with more advanced degrees of retinopathy had higher arterial pressures even at rest During exercise the differences from the controls became larger

The results obtained were discussed with regard to possible explanations and to the prognostic information that they could provide

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Haemodynamic Studies in Male Diabetics

by

TORD KARLEFORS

In a group of male patients with diabetes mellitus, it was found that a physical exercise test revealed a high frequency of abnormalities in the electrocardiogram (16) and an abnormal increase in systolic blood pressure (17) The latter occurred in patients with a duration of five years or more of diabetes It was also shown in a group of diabetics without evidence of so-called late diabetic complications that an abnormality in the systolic blood pressure could be revealed during exercise In the previous study arterial blood pressure was measured by the indirect auscultatory method

The present investigation was aimed at studying in greater detail the haemodynamic response to exercise in some of the diabetic patients previously examined The investigation involved determinations of the intra-arterial blood pressure and the cardiac output at rest and during exercise The intention was to verify the previous findings obtained with an indirect method for measuring blood pressure and to obtain additional information about the haemodynamic abnormalities in the group of diabetics examined

MATERIAL

Diabetic patients

Of the previously examined patients 41 were chosen for a more detailed investigation aiming to obtain observations on patients with as wide a range of duration of disease as possible The case numbers and the criteria used for defining retinopathy and neuropathy are the same as in the previous report (16) The exercise test in the sitting position previously performed, and the present haemodynamic investigation were not in all cases carried out in close succession to each other Therefore in a few cases the two reports may differ in the information given regarding age body weight, insulin dosage, duration of disease and degree of retinopathy of one and the same subject. For other details the reader is referred to the previous descriptions (16 17) Table I shows some clinical data As in the previous studies (16 17) the patients were divided into three groups according to duration of disease 0—4 years 5—14 years and 15 or more years referred to as D1 D2 and D3 respectively In addition they were divided into groups according to the degree of retinopathy present i e retinopathy 0 + and ++ In the previous reports (16 17) the retinopathy group +++ was included in the statistical calculations, but since only three patients with this severe form of retinopathy were studied haemodynamically statistical treatment was not carried out.

In the table presence of albuminuria at the time of examination is noted as + and ab

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In the table presence of albuminuria at the time *of* examination is noted + and ab

Table 1

Diabetic subjects Clinical data at the examination For explanation of symbols, see text

Case No	Age (years)	Height (cm)	Weight (kg)	Duration of disease (years)	Insulin requirement (I U /day)	Retinopathy	Neuropathy	Albuminuria	Serum creatinine (mg/100 ml)	Heart volume (ml/BSA)	Aorta	X ray examination Arteries in lower extremities legs	feet
2	28	169	58 6	11	68	++	+	0	1 0	445	0	0	Ca
3	34	174	71 0	7	20	+	0	+	0 7	390	L	Ca	Ca
4	30	174	80 6	20	40	++	0	0	0 9	355	0	0	0
6	22	168	58 6	7	88	0	0	0	0 9	340	0	0	0
11	37	187	81 5	14	48	+	0	0	—	360	0	0	0
12	36	176	76 6	30	54	++	0	0	0 9	440	0	0	—
14	19	187	75 1	13	58	+	0	0	—	380	0	0	—
15	44	175	76 4	17	40	++	0	0	0 7	360	0	0	0
16	43	180	84 6	17	42	++	0	0	—	310	L	0	—
18	40	173	74 0	29	44	+++	+	+	1 2	370	L	0	—
19	28	161	61 4	24	44	++	0	+	1 4	380	0	0	—
21	42	168	71 0	2	0	++	+	0	—	395	L	0	0
22	32	179	82 0	7	60	+	0	0	0 8	380	0	0	0
23	26	168	67 6	3	32	0	0	0	0 7	405	L	0	0
24	43	175	74 9	22	36	++	+	+	1 4	425	L Ca	—	—
26	36	174	63	11	40	++	0	0	1 0	370	0	0	0
27	42	180	73 8	15	56	++	+	0	0 7	360	L Ca	Ca	—
29	41	182	61 2	<1	0	0	0	0	1 0	390	0	0	0
30	19	174	61 6	14	84	++	0	0	0 7	380	0	0	—
31	23	168	61 6	10	40	+++	0	0	0 8	220	0	—	—
32	33	174	68 0	19	60	++	0	0	0 8	350	0	0	0
40	25	174	53 7	<1	24	0	0	0	1 1	245	0	0	—
44	32	178	88 5	6	40	0	0	0	1 0	370	0	0	0
46	20	182	68 2	1	28	0	0	0	0 6	400	0	0	0
50	34	171	67 8	14	76	++	+	0	0 7	475	0	0	0
52	29	167	68 0	6	46	0	0	0	0 7	430	0	0	—
54	26	175	73 7	10	64	+	0	0	0 8	370	0	0	0
56	26	166	63 5	8	60	++	0	+	0 6	375	0	0	—
59	25	168	63 4	15	44	++	+	0	—	345	0	0	0
61	25	181	68 3	11	44	++	+	0	—	360	0	0	—
66	22	171	59 3	17	56	+	0	0	—	325	0	0	—
68	40	181	70	5	32	+	0	0	0 9	400	0	Ca	0
70	18	178	63 0	2	36	0	0	0	0 6	375	0	0	—
74	26	169	62 2	16	54	0	+	0	0 8	400	0	0	—
77	37	179	79 5	<1	0	0	0	0	0 8	420	0	0	—
78	37	181	81	<1	40	0	0	0	0 9	400	0	—	—
79	40	184	99 4	16	40	+	+	0	0 8	430	0	0	0
80	23	169	70 7	21	32	+	0	0	1 0	460	0	0	—
81	43	162	66 8	33	100	+++	0	+	2 4	415	L	Ca	—
83	38	163	60	5	50	0	0	0	0 9	475	0	0	—
85	19	166	61	17	80	++	0	0	0 8	350	0	0	—

sence as 0 In case No 56 the albuminuria was not constant

Serum samples taken at about the time of examination were analysed for creatinine at the central chemical laboratory of the University Hospital Normal values are 0.6—1.2 mg/100 ml which means that patients Nos 19 24 and 81 had raised levels and patient No 18 had a value at the upper limit of normal

In all patients X ray examination of the heart and lungs was performed The cardiac volume was calculated from pictures taken in the standing position and in all cases fell within the normal range as did the form of the heart except in patient No 30 discussed in the previous report (16)

Calcifications in the aorta or the arteries of the lower leg are denoted as Ca in the table and absence as 0' If the examination had not been carried out a — is given The aorta was judged to be elongated and tortuous denoted as L in nine cases in two of these there were in addition calcifications in the aorta A simple X ray examination of the lower legs was carried out in all but three cases In four cases calcifications were judged to be located in the arteries In 19 cases the feet were also examined in this manner with positive results as regards vascular calcifications in two instances

Control subjects

The controls studied were 31 healthy men aged 19—44 years not all of whom have been described previously (16 17) but the additional ones were chosen by the same criteria The controls were divided into age groups 15—24 25—34 and 35—44 years

Comparability of diabetics and controls

The comparability in general of the various diabetic groups and the control group has

Table II

Some data for control and diabetic groups Mean values and standard deviations are given for age duration of disease height weight and body surface area (BSA)

		n	Age (years)		Duration of disease (years)		Height (cm)		Weight (kg)		BSA (m²)	
			Mean	S D	Mean	S D	Mean	S D	Mean	S D	Mean	S D
	Age group (years)											
Control subjects	15—24	11	21.2	1.33	—	—	180.9	2.91	70.1	4.12	1.89	0.0568
	25—34	11	30.9	3.27	—	—	180.5	3.11	74.0	14.93	1.92	0.162
	35—44	9	40.0	3.12	—	—	175.5	6.86	73.4	7.46	1.88	0.131
	15—44	31	30.1	8.10	—	—	179.2	4.94	72.4	9.90	1.90	0.121
Diabetic subjects	D1	8	30.8	9.59	1.0	1.19	176.4	5.80	68.2	9.15	1.83	0.117
	D2	17	29.4	6.61	9.3	3.26	174.2	7.15	69.0	8.82	1.82	0.139
	D3	16	33.6	8.82	20.4	5.60	172.3	6.34	72.1	10.48	1.84	0.154
	0	12	29.3	7.66	3.8	4.61	174.0	6.70	67.6	10.36	1.80	0.143
	+	9	30.3	8.05	12.1	5.35	178.5	6.75	75.9	11.11	1.93	0.156
	++	17	32.5	8.39	15.8	6.42	172.4	5.52	69.1	7.65	1.81	0.114

been discussed previously (16, 17) Table II shows the mean values for age in the diabetic patients, grouped according to retinopathy or duration of disease, and for the controls, divided into age groups and in a combined group The same table shows the duration of disease in the diabetic patients It is apparent from the table that the average age in the groups D1, D2 and D3 (31, 29 and 34 years, respectively) and the three retinopathy groups (29, 30 and 33 years) does not differ much from that in the combined control group (30 years) The median values for age do not indicate unevenness in age distribution within the groups

Table II shows that the values for height, weight and body surface area in the diabetic groups D1, D2 and D3 were slightly smaller than those in the combined control group, except that D3 was practically identical with the controls as regards weight However, differences between these diabetic groups and the control group were not significant The retinopathy groups, too, had a slightly smaller body surface area than the control group, except group + The mean height in this group was about the same as in the control group but the body weight was higher Mean values for height and weight in the other retinopathy groups were slightly smaller than in the control group

An estimation of the skeletal weight was obtained from the body height and the skeletal measurements of radio ulnar breadth and breadth of the femoral condyle The calculation was made according to von Dobeln, Saltin and Stenberg, 1963 (10) Skeletal weight is said to represent about 20 per cent of the lean body mass and since the latter has a relatively constant composition the ratio between body weight (W) and skeletal weight (S) may be useful for evaluation of overweight (11) This ratio normally varies between 5 0 and 6 0 although values slightly over 6 0 may be seen in individuals with a well developed musculature (11)

Table III shows skeletal weight and the ratio body weight/skeletal weight (W/S), in the diabetic groups, D1, D2 and D3, and the control group It can be seen from the table that this ratio is 6 0 in the controls and 5 6 5 9 and 6 4 respectively in the diabetic groups

It is not likely that the small differences described above as regards height weight, surface area and skeletal weight can account for the haemodynamic differences between the different diabetic groups and the controls

Table III

Estimated skeletal weight (S) and ratio weight/skeletal weight (W/S) in control group and in diabetic subjects grouped according to duration of disease Mean values and standard deviations are given

	n	S		W/S	
		Mean	S D	Mean	S D
Control	23	12 47	1 16	5 98	0 748
D1	7	12 01	0 955	5 64	0 716
D2	16	11 86	1 47	5 86	0 642
D3	15	11 45	1 48	6 37	0 565

METHODS

The subjects were examined in the morning All patients treated with insulin had taken their ordinary dose at about 7 a m with the exception of case 18 who was not given any insulin All subjects had eaten a light breakfast at about 07 30 except for case 21 who was fasting Under local anaesthesia with mepi

vacain (1 per cent Carbocain Bofors Sweden) polythene tubes (outer diameter 1 57 mm inner diameter 1 14 mm) were inserted into one brachial artery (usually the left) and into a cubital vein (usually in the right arm) The latter tube was advanced to the subclavian vein The technique was similar to that de scribed by Berneus Carlsten Holmgren and Seldinger 1954 (4) The subjects were allowed to rest for at least 30 minutes before the measurements were taken between 09.30 and 11 00 i e about 2—3 ½ hours after breakfast

Arterial pressure was registered by an in ductance manometer and mean pressures were obtained by electrical integration using the equipment of Elema Stockholm Sweden Two electrocardiographic chest leads were used for simultaneous recordings.

Cardiac output was measured with the in dicator dilution technique using bromsulpha lein as indicator (25) Injections were given in the subclavian vein and arterial blood samples obtained at one second intervals by free flow from the arterial tube into hepari nized test tubes in a rotating disc The stand ard deviation of the differences between dup licate determinations of cardiac output was 9 per cent (i e the coefficient of variation) This figure is based upon measurements at rest and during exercise and probably con tains a small systematic biological error

Circulatory measurements were made at rest and during exercise of varying intensity The exercise consisted of bicycling in the supine position the bicycle ergometer constructed by Holmgren and Mattsson 1954 being used (13) The first load of exercise was 300 kpm/min and in most cases a second set of measurements were also made during a second load 600 kpm/min following directly after the first one The haemodynamic observations given in the tables were obtained during a circula tory steady state at the 4th 8th minute of exercise at each load using the same criteria as in the previous paper (17)

Expired air was collected in Douglas bags and analysed for O and CO_2 content by the Scholander technique (21) The Astrup micro-technique as described by Siggaard Andersen 1962 (22) was used to determine the pH pCO_2 and standard bicarbonate in arterial blood Oxygen saturation in arterial blood was determined spectrophotometrically as de scribed by Holmgren and Pernow 1959 (14) Haemoglobin concentration was determined spectrophotometrically after conversion to cyanmethaemoglobin

Blood glucose was determined by the glu cose oxidase method (19) The analyses were made at the laboratory of the local Diabetes Detection Campaign For reasons discussed previously (17) only values for samples stor ed at $+4°$ C were considered Values for other samples have been marked by an asterisk in the tables

The same statistical methods as used pre viously (17) have been applied In addition Wilcoxon s T test for paired observations has been used (26) For the main part only means and standard deviations are given in the tab-les since there were no great discrepancies between the means and the medians except as regards blood sugar values where both of them are given together with standard devia tions and interquartile ranges

In the statistical calculations the values ob-tained at the highest work load in the diabe tic subjects Nos 3 and 27 have been rejected The former was not in a circulatory steady state and for the latter the highest work load was not 600 kpm/min but probably 700 kpm/min as a result of a technical mistake It has nevertheless been regarded as worth while to give these values

Table IV gives information on the alterna tive hypothesis one sided or two sided and the variables compared Column C repre sents the comparison between the different age groups of the control subjects The co-lumns D_{dur} and $D_{ret.}$ represent the comparison within the diabetic groups of different duration of disease and degree of retinopathy respectively Columns C-D_{dur} and C D_{ret}" represent the comparison bet ween the control group and diabetic group of different duration of disease and between the former and the retinopathy groups re spectively For the one sided alternative hy pothesis the following assumptions have been made 1) *heart rate* — higher in younger age

Table IV

Alternative hypothesis for values obtained at rest (R) and during exercise (E)
1 = one-sided alternative hypothesis
2 = two-sided alternative hypothesis
— = no test performed
For further explanation, see text

Variable	C		D_{dur}		D_{ret}		$C—D_{dur}$		$C—D_{ret}$	
	R	E	R	E	R	E	R	E	R	E
Heart rate	2	1	2	1	2	1	2	1	2	1
Cardiac output	2	2	2	1	2	1	2	1	2	1
Stroke volume	2	2	2	1	2	1	2	1	2	1
Syst blood pressure	1	1	1	1	1	1	1	1	1	1
Diast blood pressure	1	1	1	1	1	1	1	1	1	1
Mean blood pressure	1	1	1	1	1	1	1	1	1	1
Calc vascular resist	1	1	1	1	1	1	1	1	1	1
Oxygen uptake	2	2	2	2	2	2	2	2	2	2
A—v O diff	—	—	2	1	—	—	2	1	—	—
Art CO tension	—	—	2	2	—	—	2	1	—	—
Stand bicarb	—	—	2	2	—	—	2	1	—	—
pH	—	—	2	2	—	—	2	1	—	—
Haematocrit value	—	—	2	2	—	—	2	2	—	—
Haemoglob conc	—	—	2	2	—	—	2	2	—	—
Art O satur	—	—	2	2	—	—	2	2	—	—
Ventilation	—	—	2	2	—	—	2	2	—	—
RQ	—	—	2	2	—	—	2	2	—	—
Blood sugar	—	—	2	2	2	2	1	1	1	1

groups, in diabetic groups of longer duration of disease, with increasing degree of retinopathy, in diabetic groups as compared with the control group 2) *cardiac output and stroke volume* — lower in diabetic groups of longer duration of disease, with increasing degree of retinopathy, in diabetic groups as compared with the control group 3) *intra-arterial pressures and calculated vascular resistance* — higher in older age groups, in diabetic groups of longer duration of disease, with increasing degree of retinopathy, in diabetic groups as compared with the control group 4) *calculated arterio venous oxygen difference* — higher in diabetic groups of longer duration of disease in diabetic groups as compared with the control group 5) *arterial carbon dioxide tension standard bicarbonate and pH* — lower in the diabetic groups than in the control group 6) *blood sugar* — higher in the diabetic groups than in the control group

Conventional probability levels of significance have been used and marked in the tables with the following symbols

0 $p > 0.05$ (not significant)
* $0.01 < p < 0.05$ (almost significant)
** $0.001 < p < 0.01$ (significant)
*** $p < 0.001$ (highly significant)
— no test performed

RESULTS

All values for the diabetics are given in Tables V and VI (se pages 74 and 77) Individual values for the control subjects may be obtained from the author

Table VII

Observations in control subjects grouped according to age Mean values and standard deviations for heart rate cardiac output and stroke volume, at rest and at differens work loads are given

	Age group (years)	Heart rate (beats/min) n	Mean	S D	Cardiac output (l/min) n	Mean	S D	Stroke volume (ml) n	Mean	S D
Rest	15—24	11	67.4	7.15	11	7.1	1.07	11	105.1	11.11
	25—34	11	63.6	9.20	11	6.8	0.947	11	108.4	20.03
	35—44	9	64.3	8.40	9	6.5	1.38	9	100.7	17.52
	15—44	31	65.2	8.18	[illegible]	6.8	1.12	31	105.0	16.32
300 (kpm/min)	15—24	11	101.3	4.17	11	12.3	1.55	11	121.3	15.53
	25—34	11	101.1	9.22	11	12.5	1.42	11	125.2	18.62
	35—44	9	97.6	12.63	9	11.1	2.02	9	113.6	15.48
	15—44	31	100.1	8.92	31	12.0	1.72	31	120.4	16.81
600 (kpm/min)	15—24	9	130.6	6.65	9	15.0	1.76	9	114.7	12.94
	25—34	8	123.8	13.10	7	17.0	1.81	7	136.1	26.71
	35—44	9	130.6	17.85	9	15.4	1.93	9	119.7	16.63
	15—44	26	128.5	13.21	25	15.7	1.95	25	122.5	20.17

A. Heart rate, cardiac output and stroke volume at rest and during exercise

I Controls

Table VII shows the values in the different age groups 15—24, 25—34 and 35—44 years and in the combined age group 15—44 years, which will be used later for comparison with the different diabetic groups There were no significant differences among the age groups

II a Diabetic subjects grouped according to duration of disease

Table VIII shows the values in the control group and in D1 D2 and D3

The heart rate was slightly higher in groups D1 and D3 than in the control group but the differences were not significant except that at rest the difference between the control group and D3 was probably significant

The cardiac output at rest was about the same in diabetics and controls, but during exercise at a work load of 300 kpm/min, the cardiac output was significantly lower in groups D2 and D3 At the higher work load, 600 kpm/min all the groups of diabetics had a lower cardiac output than the control group The differences were significant at various levels (see Table VIII)

The stroke volume was lower in the diabetic groups at rest as well as during exercise The statistical comparison showed various levels of significance (see Table VIII) between the control group and the groups D2 and D3 at rest and at 300 kpm/min but not between the controls and the group D1

Table VIII

Observations in combined control group and in diabetic subjects grouped according to duration of disease Mean values, standard deviations and significances for differences from control group are given for heart rate, cardiac output and stroke volume, at rest and at different work loads

		Heart rate (beats/min)				Cardiac output (l/min)				Stroke volume (ml)			
		n	Mean	SD	Significance for diff from contr	n	Mean	SD	Significance for diff from contr	n	Mean	SD	Significance for diff from contr
Rest	Controls	31	65 2	8 18	—	31	6 8	1 12	—	31	105 0	16 32	—
	D1	8	71 0	11 51	[illegible]	7	7 2	1 24	0	7	101 0	14 35	0
	D2	17	68 3	12 09	0	17	6 3	1 48	[illegible]	17	93 5	19 00	*
	D3	16	74 8	14 83	[illegible]	16	6 4	0 951	[illegible]	16	88 5	17 22	**
300 kpm/min	Controls	31	100 1	8 92	—	31	12 0	1 72	—	31	120 4	16 81	—
	D1	8	106 9	13 89	0	7	11 4	2 01	0	7	108 7	17 52	0
	D2	17	99 7	10 05	0	17	10 1	1 64	***	17	102 3	16 47	**
	D3	16	106 1	16 30	0	16	10 4	1 17	*	16	100 1	17 79	*
600 kpm/min	Controls	26	128 5	13 21	—	25	15 7	1 95	—	25	122 5	20 17	—
	D1	8	138 9	20 35	0	6	14 2	2 34	*	[illegible]	105 8	10 23	**
	D2	15	129 9	15 57	0	14	13 5	1 63	**	14	104 7	14 96	**
	D3	13	135 5	13 73	0	13	13 5	2 14	**	13	100 7	19 94	**

At 600 kpm/min the differences from the controls were significant for all the diabetic groups

The lower cardiac output in the diabetics, *especially during exercise on* the highest work load, was thus due to a smaller stroke volume

There were no statistically significant differences between the diabetic groups as regards heart rate, cardiac output or stroke volume

II b Diabetic subjects grouped according to retinopathy

Table IX shows the values in the control group and in the retinopathy groups 0, + and ++ The individual values for the three diabetic subjects (cases Nos 18, 31 and 81) with retinopathy graded as +++ are given in Table V

The heart rate at rest and during exercise was *slightly higher in the* group ++ than in the control group, the differences being significant at various levels at rest and at *600 kpm/min* The differences between the control group and the retinopathy group [illegible] were small and not significant For some reason the group + *had a slightly* lower heart rate than the control group the *difference* being probably significant at 300 kpm/min

A comparison of the retinopathy

Table IX

Observations in combined control group and in diabetic subjects grouped according to retinopathy (0, + and ++) Mean values standard deviations and significances for differences from control group are given for heart rate, cardiac output and stroke volume at rest and at different work loads

		Heart rate (beats/min)				Cardiac output (l/min)				Stroke volume (ml)			
		n	Mean	SD	Significance for diff from contr	n	Mean	SD	Significance for diff from contr	n	Mean	SD	Significance for diff from contr
Rest	Controls	31	65.2	8.18	—	31	6.8	1.12	—	31	105.0	16.32	—
	0	12	69.3	10.97	0	11	6.7	0.947	0	11	97.5	13.97	0
	+	9	64.1	10.19	0	9	6.8	1.60	0	9	106.9	18.26	0
	++	17	75.4	13.43	**	17	6.4	1.21	0	17	83.6	15.04	***
300 kpm/min	Controls	31	100.1	8.92	—	31	12.0	1.72	—	31	120.4	16.81	—
	0	12	104.5	12.80	0	11	11.2	1.98	0	11	108.7	16.59	0
	+	9	94.3	9.73	*	9	10.0	1.53	*	9	107.0	18.57	0
	++	17	107.1	14.21	0	17	10.5	1.14	**	17	99.7	15.16	***
600 kpm/min	Controls	26	128.5	13.21	—	25	15.7	1.95	—	25	122.5	20.17	—
	0	12	136.0	17.32	0	11	14.4	1.95	*	11	107.2	11.63	**
	+	8	120.9	11.74	0	8	13.5	1.79	**	8	112.1	12.62	0
	++	15	139.1	14.50	*	13	13.3	1.76	***	13	97.0	17.49	***

groups 0 + and ++ with one another showed that at rest and at 300 kpm/min the group ++ had a probably significantly higher heart rate than the group + On the same work load the heart rate in the group 0 was probably significantly higher than in the group + At 600 kpm/min the difference between these two groups was of the same significance and the group ++ had a significantly higher heart rate than the group + On the whole it can perhaps be said that there was no distinct tendency for increasing grades of retinopathy to be associated with higher heart rates during exercise

The cardiac output at rest was about the same in the retinopathy groups as in the control group During exercise the diabetic groups again showed lower values especially at the highest work load At 300 kpm/min the difference between controls and group 0 was not significant but otherwise there were statistically significant differences at various levels (see Table IX)

A comparison of the retinopathy groups with one another as to the cardiac output showed that the values at

Table VIII

Observations in combined control group and in diabetic subjects grouped according to duration of disease Mean values, standard deviations and significances for differences from control group are given for heart rate, cardiac output and stroke volume, at rest and at different work loads

		Heart rate (beats/min)				Cardiac output (l/min)				Stroke volume (ml)			
		n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr
Rest	Controls	31	65 2	8 18	—	31	6 8	1 12	—	31	105 0	16.32	—
	D1	8	71 0	11 51	■	7	7 2	1 24	■	7	101 0	14 35	0
	D2	17	68 3	12 09	0	17	6 3	1 48	0	17	93 5	19 00	*
	D3	16	74 9	14 83	*	16	6 4	0 951	0	16	88 5	17 22	**
300 kpm/min	Controls	31	100 1	8 92	—	31	12 0	1 72	—	31	120 4	16 81	—
	D1	8	106 9	13 89	■	7	11 4	2 01	0	7	108 7	17 52	0
	D2	17	99 7	10 05	0	17	10 1	1 64	**	17	102 3	16 47	**
	D3	16	106 1	16 30	0	16	10 4	1 17	**	16	100 1	17 79	**
600 kpm/min	Controls	26	128 5	13 21	—	25	15 7	1 95	—	25	122 5	20 17	—
	D1	8	138 9	20 35	0	6	14 2	2 34	*	6	105 8	10.23	**
	D2	15	129 9	15 57	0	14	13 5	1 63	**	14	104 7	14 96	**
	D3	13	135 5	13 73	0	13	13 5	2 14	*	13	100 7	19 94	**

At 600 kpm/min the differences from the controls were significant for all the diabetic groups

The lower cardiac output in the diabetics, especially during exercise on the highest work load, was thus due to a smaller stroke volume

There were no statistically significant differences between the diabetic groups as regards heart rate, cardiac output or stroke volume

II b Diabetic subjects grouped according to retinopathy

Table IX shows the values in the control group and in the retinopathy groups 0, + and ++ The individual values for the three diabetic subjects (cases Nos 18, 31 and 81) with retinopathy graded as +++ are given in Table V

The heart rate at rest and during exercise was slightly higher in the group ++ than in the control group, the differences being significant at various levels at rest and at 600 kpm/min The differences between the control group and the retinopathy group ■ were small and not significant For some reason the group + had a slightly lower heart rate than the control group the difference being probably significant at 300 kpm/min

A comparison of the retinopathy

The systolic blood pressure tended to be higher in the oldest age group compared with the youngest, but there were no statistically significant differences between the age groups

The same was true for the diastolic blood pressure However, the statistical comparison showed that at rest the difference between the oldest age group and the youngest was probably significant, and at 300 kpm/min the diastolic pressure of the youngest group was probably significantly lower than in both the intermediate and the oldest group At 600 kpm/min there were no significant differences

The mean arterial blood pressure tended to be higher in the oldest age group and probably significantly different from the youngest at rest and at 300 kpm/min At 600 kpm/min there were no significant differences

II a Diabetic subjects grouped according to duration of disease

Table XI shows the values for the control group and for the diabetic groups D1, D2 and D3

There were no appreciable differences between the values obtained for systolic, diastolic and mean arterial blood pressures in the control group and diabetic group D1 either at rest or

Table XI

Observations in combined control group and in diabetic subjects grouped according to duration of disease Mean values, standard deviations and significances for differences from control group are given for systolic, diastolic and mean arterial pressures at rest and at different work loads

			Systolic (mm Hg)			Diastolic (mm Hg)			Mean (mm Hg)		
		n	Mean	S.D	Significance for diff from contr	Mean	S.D	Significance for diff from contr	Mean	S D	Significance for diff from contr
Rest	Controls	31	121.0	10.57	—	68.1	7.82	—	88.3	10.11	—
	D1	8	121.1	8.71	0	69.1	5.00	0	90.0	6.76	0
	D2	17	125.5	10.49	0	73.1	6.52	**	95.4	7.92	*
	D3	16	136.9	21.09	**	77.4	11.05	**	101.6	15.50	**
300 kpm/min	Controls	31	142.7	14.76	—	74.7	9.37	—	95.5	13.16	—
	D1	8	139.1	13.53	0	69.5	6.21	0	96.9	6.60	0
	D2	17	151.8	18.15	*	81.2	10.94	*	108.9	14.64	*
	D3	16	168.9	24.19	***	86.1	10.32	**	117.4	16.52	***
600 kpm/min	Controls	26	162.4	17.24	—	78.3	10.19	—	109.0	13.73	—
	D1	8	163.4	19.67	0	79.8	6.23	0	110.8	9.56	0
	D2	15	176.7	20.51	*	89.1	10.31	**	120.3	13.34	**
	D3	13	197.1	24.27	***	94.8	13.31	***	132.8	20.26	**

rest were about the same, but during exercise the cardiac output tended to be smaller with increasing grade of retinopathy However, the differences were not statistically significant

During exercise the stroke volumes, too, were lower in the retinopathy groups but the statistical comparison showed that all differences were not significant in all cases (see Table IX) The cardiac output and stroke volumes of the three patients with retinopathy +++ were low, especially during work

At rest and during exercise the stroke volume of the retinopathy group ++ tended to be smaller than in the groups 0 and + The statistical comparison showed that the difference between the groups ++ and + at rest was significant On 600 kpm/min the differences were probably significant Neither at rest nor during exercise was there any significant difference between the retinopathy group 0 and the group +

B Systolic, diastolic and mean arterial blood pressure at rest and during exercise

1 Controls

Table X shows the values for the different age groups 15—24, 25—34 and 35—44 years and in the combined age group 15—44 years, which will later be used for comparison with the different diabetic groups

Table X

Observations in control subjects grouped according to age Mean values and standard deviations for systolic, diastolic and mean arterial pressures, at rest and at different work loads are given

	Age group (years)	n	Systolic (mm Hg) Mean	Systolic SD	Diastolic (mm Hg) Mean	Diastolic SD	Mean (mm Hg) Mean	Mean SD
Rest	15—24	11	119 6	7 02	65 2	5 86	84 1	7 80
	25—34	11	120 5	8 70	68 1	7 41	88 1	9 27
	35—44	9	123 4	15 90	71 8	9 54	93 7	11 95
	15—44	31	121 0	10 57	68 1	7 82	88 3	10 11
300 kpm/min	15—24	11	140 7	8 49	70 3	7 42	93 6	10 59
	25—34	11	143 7	19 31	77 2	10 82	100 1	12 02
	35—44	9	143 9	15 88	77 0	8 51	105 9	15 33
	15—44	31	142 7	14 76	74 7	9 37	99 5	13 16
600 kpm/min	15—24	9	159 8	19 79	74 1	10 81	103 0	13 96
	25—34	8	163 6	12 28	78 1	8 79	108 6	9 38
	35—44	9	164 0	19 84	82 8	9 90	115 2	15 26
	15—44	26	162 4	17 24	78 3	10 19	109 0	13 73

Table XII

Observations in combined control group and in diabetic subjects grouped according to retinopathy Mean values, standard deviations and significances for differences from control group are given for systolic, diastolic and mean arterial pressures, at rest and at different work loads

			Systolic (mm Hg)			Diastolic (mm Hg)			Mean (mm Hg)		
		n	Mean	S D	Significance for diff from contr	Mean	S D	Significance for diff from contr	Mean	S D	Significance for diff from contr
Rest	Controls	31	121.0	10.57	—	68.1	7.82	—	88.3	10.11	—
	0	12	124.8	10.36	0	71.4	7.06	0	92.4	8.85	0
	+	9	124.9	9.58	0	71.8	7.53	0	93.8	8.18	■
	++	17	128.6	14.88	0	74.8	7.46	**	97.4	9.21	**
300 kpm/min	Controls	31	142.7	14.76	—	74.7	9.37	—	99.5	13.16	—
	0	12	142.7	17.02	0	75.4	9.55	0	101.6	10.99	■
	+	9	148.7	18.34	0	79.4	14.06	0	107.3	18.30	0
	++	17	162.9	20.10	***	83.2	9.42	**	113.8	12.67	***
600 kpm/min	Controls	26	162.4	17.24	—	78.3	10.19	—	109.0	13.73	—
	0	12	169.6	24.67	0	85.6	11.91	■	116.3	16.12	0
	+	8	175.0	21.03	■	84.6	7.71	0	115.1	9.16	0
	++	15	189.2	18.48	***	91.9	10.16	***	128.0	13.10	***

In group ++ the systolic blood pressure tended to be higher than in the control group even at rest, and during exercise the difference increased and became highly significant There was no significant difference between the control group and the groups 0 and + although these had higher values at 600 kpm/min

As regards the diastolic pressure the situation was about the same except that the difference between the control group and the retinopathy group ++ was significant even at rest At 300 kpm/min the difference was significant too and at 600 kpm/min highly significant

The mean arterial blood pressure at rest and during exercise tended to be a little higher in the retinopathy groups 0 and + as compared with the control group, but the differences were not statistically significant However, at rest the mean pressure was significantly higher in group ++ as compared with the control group and during exercise the differences were highly significant

To sum up, there were no statistically significant blood pressure differences between the retinopathy groups 0 and + on one hand and the control group on the other, either at rest or during exercise The retinopathy group

during exercise In groups D2 and D3 the systolic pressure was higher At rest only the difference between the control group and group D3 was significant, but during exercise probably significant differences appeared also between the former and group D2

Again, with increasing duration of disease the diastolic pressure became higher The differences from the control group had various levels of significance (see Table XI) The same was true for the mean arterial pressure For information of the levels of significance see Table XI

To sum up, there were no significant differences in arterial blood pressure between the control group and the diabetic group with the shortest duration of disease, 0—4 years, D1, either at rest or during exercise With increasing disease duration the blood pressure became higher It may also be said that circulatory strain made it easier to reveal the abnormal blood pressure conditions in these groups In group D2 a probably significant difference from the control value for the systolic pressure first appeared during exercise This corresponds with the findings in a previous paper (17), where it was shown that the use of a simple exercise test made it possible to reveal an abnormally high systolic blood pressure more easily than by observations at rest

A comparison of groups D1, D2 and D3 with one another showed that those who had been diabetic for 15 years or more, D3, had already at rest a systolic blood pressure which was probably significantly higher than those with the shortest history of the disease, D1 The differences between these two groups were highly significant at the work load 300 kpm/min and significant at 600 kpm/min During exercise, but not at rest, the systolic pressure was probably significantly higher in group D3 than in D2 There was no significant difference between groups D1 and D2

As regards the diastolic pressure, this tended to be higher in groups with longer disease duration At rest the differences were not significant At 300 kpm/min group D2 as well as D3 had a highly significantly higher diastolic pressure than D1, but at 600 kpm/min, only D3 gave such a result

Also, the mean arterial blood pressure was higher in groups with longer durations of disease than in the group with the shortest one At rest only the difference between the groups D3 and D1 were probably significant At 300 kpm/min group D2 as well as D3 had kpm/min the difference between these two groups was highly significant and at 600 kpm/min significant The difference between groups D2 and D1 was significant at 300 kpm/min but not at 600 kpm/min

II b Diabetic subjects grouped according to retinopathy

Table XII shows the values in the control group and the retinopathy groups 0, + and ++ The individual values for the three diabetic subjects (cases Nos 18, 31 and 81) with retinopathy graded as +++ are given in Table V

Table XIII

Observations in control subjects grouped according to age Mean values and standard deviations for calculated vascular resistance [mean arterial blood pressure (mm Hg)/cardiac ou put (l/min)] at rest and at different work loads are given

	Age group (years)	n	Cal vasc resist Mean	S D
Rest	15—24	11	12.2	2.50
	25—34	11	13.3	2.69
	35—44	9	15.1	3.69
	15—44	31	13.4	3.08
300 kpm/min	15—24	11	7.7	1.22
	25—34	11	8.0	1.16
	35—44	9	9.8	2.13
	15—44	31	8.4	1.72
600 kpm/min	15—24	9	7.0	1.08
	25—34	7	6.5	1.02
	35—44	9	7.6	1.45
	15—44	25	7.1	1.24

There were no obvious differences in SVR between the control group and the diabetic group D1, but with increasing duration of disease there was a tendency to higher SVR which was apparent even at rest The differences had various levels of significance (see Table XIV)

The same was true even if the comparison was made within the diabetic groups At rest the difference between the groups D1 and D3 was probably significant, at 300 kpm/min this difference was highly significant and the difference between the former and the group D2 was probably significant

At 600 kpm/min the differences between D1 and D2 and between D1 and D3 were probably significant Neither at rest nor during exercise were there any significant differences between D2 and D3

The relation between mean arterial blood pressure and cardiac output at rest and during exercise in the control group and in the diabetic groups is shown in Fig 1

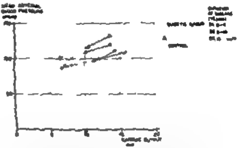

Fig 1 Mean arterial blood pressure in relationship to cardiac output at rest and at 300 and 600 kpm/min in diabetic subjects grouped according to duration of disease and in the control group

II b Diabetic subjects grouped according to retinopathy

Table XV shows the values in the control group and in the retinopathy groups 0 + and + +

Compared with the control group, the SVR tended to be higher in all the retinopathy groups, especially in the group + + Table XV shows that there were increasingly significant differences with increasing work load and at the highest work load all differences from the control group were significant The SVR of the patients with retinopathy + + + cases Nos 18 31

+ + had a significantly higher systolic blood pressure only during exercise, while the diastolic and the mean pressures were significantly higher even at rest Two of the three patients with retinopathy + + + (cases Nos 18 and 81) had high pressures already at rest, whereas the third one (case No 31) did not differ much from the controls

A comparison of the retinopathy groups 0 and + with one another showed that there were no significant differences in blood pressure either at rest or during exercise There was, however, a tendency to increasing blood pressure in the group with the moderate form of retinopathy, + +, compared with the two other retinopathy groups As regards the systolic blood pressure, the differences were not significant at rest At 300 kpm/min the difference between the groups 0 and + + was significant, and probably significant between the latter and group + At 600 kpm/min there was only one statistically probable significant difference, namely between the groups 0 and + +

As regards the diastolic blood pressure the situation was about the same with no significant differences at rest, but at 300 kpm/min the differences were probably significant At 600 kpm/min the outcome of the comparison was the same as for the systolic pressure

There were no significant differences in mean arterial blood pressure at rest within the retinopathy groups At 300 kpm/min the differences between groups 0 and + + and groups + and + + were probably significant, at 600 kpm/min the former difference was probably significant and the latter, significant

To summarize, it may again be said that circulatory strain revealed differences in blood pressure which were not easily recognized at rest

C Calculated vascular resistance at rest and during exercise

The total vascular resistance in the systemic circulation (SVR) has been calculated as a quotient between the *mean arterial blood pressure (mm Hg)* and the cardiac output *(l/min) It is understood* that this quotient may not give a value for flow resistance in a strict physical sense, but in the present connection it was merely used as a convenient expression for the relation between pressure and flow

I Controls

Table XIII shows the values in the different age groups 15—24, 25—34 and 35—44 years and in the combined age group 15—44 years, which will be used later for comparison with the different diabetic groups

The SVR tended to become slightly higher with increasing age The differences between the youngest and the oldest group were probably significant at rest, and significant at 300 kpm/min

II a Diabetic subjects grouped according to duration of disease

Table XIV shows the values in the control group and in the diabetic groups *D1, D2* and *D3*

Table XV

Observations in combined control group and in diabetic subjects grouped according to retinopathy Mean values and standard deviations for calculated vascular resistance calculated arterio venous oxygen difference and oxygen uptake at rest and at different work loads are given In addition significances for differences from control group for calculated vascular resistance and oxygen uptake are given

		Calc vasc res st				Calc a v O₂ d ff (ml/l)			Oxygen uptake (ml min)			
		n	Mean	S D	S gn f cance for d ff from contr	n	Mean	S D	n	Mean	S D	S gn f cance for d ff from contr
Rest	Controls	31	13 4	3 08	—	31	41 5	7 38	31	277	44 73	—
	0	11	14 2	2 94	0	10	44 5	6 82	11	290	30 36	■
	+	9	14 5	4 34	0	9	45 8	11 34	9	302	56 78	*
	++	17	15 9	3 85	*	17	46 9	8 80	17	290	39 17	0
300 kpm m n	Controls	31	8 4	1 72	—	30	79 8	13 28	30	948	103 08	—
	0	11	9 4	2 18	0	11	83 6	12 88	11	917	93 67	0
	+	9	10 9	3 0[illegible]	*	9	91 2	14 48	9	898	106 16	0
	++	17	10 9	1 65	* *	16	91 8	10 43	16	949	89 86	0
600 kpm m n	Control	25	7 1	1 24	—	24	97 9	15 02	24	1506	128 57	—
	0	11	8 3	1 63	*	11	104 4	14 57	12	1493	173 96	0
	+	8	8 6	1 14	***	8	114 1	11 18	8	1531	144 10	■
	++	13	9 9	1 78	*	11	119 7	24 02	12	1581	235 01	■

take (ml/min) and the cardiac output (l/min)

I Controls

The mean values in the different age groups 15—24 25—34 and 35—44 years were approximately the same and are therefore not given separately The values for the combined group 15—44 years are shown in Table XIV

II a Diabetic subjects grouped according to duration of disease

Table XIV shows the values in the control group and in the groups D1 D2 and D3

The oxygen uptake was about the same in the control group and in the diabetic groups The statistical comparison showed that the value in group D2 was probably significantly higher at rest than that of the control group but at 300 kpm/min it was lower with the same degree of significance The differences although significant were too small to infer that these two groups had performed work of different intensity Moreover no differences in oxygen uptake were observed at the higher work load There were no significant differences between the duration groups

Table XIV

Observations in combined control group and in diabetic subjects grouped according to duration of disease Mean values, standard deviations and significances for differences from control group are given for calculated vascular restistance, calculated arterio-venous oxygen difference and oxygen uptake at rest and at different work loads

		Calc vasc resist				Calc a v O diff (ml/l)				Oxygen uptake (ml/min)			
		n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr
Rest	Controls	31	13 4	3 08	—	31	41.5	7 38	—	31	277	44 73	—
	D1	7	13 0	2 80	0	6	40 8	5 85	0	7	283	24 99	0
	D2	17	15 9	4 11	*	17	49 5	9 05	**	17	304	38 88	
	D3	16	16 2	3 98	**	16	44 8	8 76	0	16	283	45 69	0
300 kpm/min	Controls	31	8 4	1 72	—	30	79 8	13 28	—	30	948	103 08	—
	D1	7	8 6	1 50	0	7	85 1	12 28	0	7	950	43 33	0
	D2	17	11 1	2 54	***	17	90 5	14 49	**	17	900	89 62	*
	D3	16	11 5	2 67	***	15	92 5	13 65	**	15	945	143 46	0
600 kpm/min	Controls	25	7 1	1 24	—	24	97 9	15 02	—	24	1506	128 57	—
	D1	6	7 8	1 28	0	6	103 0	12 74	0	8	1511	195 54	0
	D2	14	9 1	1 49	***	13	114 8	19 68	**	13	1538	198 32	0
	D3	13	10 2	3 02	***	12	117 8	21 03	**	12	1545	188 41	0

and 81 were at rest 17 8, 22 4 and 22 7, respectively, compared with 13 4 in the control group At 300 kpm/min the corresponding values were 14 7, 12 1 and 18 6 respectively, compared with 8 4 in the control group Thus, the SVR during work was obviously increased in these patients, even in the one who did not differ much from the control group as regards mean arterial pressure

The increased calculated SVR in the groups 0 and + during the work load of 600 kpm/min was the result of the lower cardiac output of these two groups, since the mean arterial pressures of the groups did not significantly differ from that of the control group

A comparison of the SVR among the retinopathy groups showed a tendency to increased values in the group ++ At rest, the difference from group 0 was not significant, but during exercise these differences became probably significant There were no significant differences between the groups 0 and +

D Oxygen uptake and calculated arterio-venous oxygen difference at rest and during exercise

The arterio-venous oxygen difference (a—v difference) has been calculated as a quotient between the oxygen up-

Table XVI

Observations in combined control group and in diabetic subjects grouped according to duration of disease Mean values, standard deviations and significances for differences from control group are given for ventilation, respiratory quotient and blood sugar, at rest and at different work loads In addition medians and interquartile ranges (Q_3—Q_1) for blood sugar values are given

		Ventilation (l/min)				RQ				Blood sugar (mg/100ml)					
		n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr	n	Mean	Median	S D	Q_3 Q_1	Significance for diff from contr
Rest	Controls	31	7.2	1.37	—	31	0.79	0.0659	—	14	74.5	76.5	21.40	22.00	—
	D1	7	7.4	0.765	0	7	0.79	0.0586	0	3	145.0	139.0	74.18	—	—
	D2	17	8.1	1.76	0	17	0.81	0.0758	0	8	187.0	189.5	61.78	92.75	***
	D3	15	8.2	1.67	-	16	0.80	0.0608	0	10	194.7	197.5	80.99	118.00	***
300 kpm/min	Controls	30	20.4	2.90	—	30	0.83	0.0507	—	13	75.0	77.0	8.12	9.50	—
	D1	7	21.3	2.14	0	7	0.84	0.0300	0	3	134.7	122.0	70.85	—	—
	D2	17	19.2	2.62	0	17	0.83	0.0551	0	8	173.4	173.5	64.73	100.00	***
	D3	14	20.8	4.28	0	15	0.83	0.0484	0	10	179.4	176.5	78.28	114.00	***
600 kpm/min	Controls	24	35.4	6.44	—	24	0.93	0.0614	—	13	75.4	76.0	8.12	11.00	—
	D1	8	37.3	6.08	0	8	0.94	0.0778	0	3	125.7	96.0	48.50	—	—
	D2	13	35.8	4.97	0	13	0.91	0.0743	0	8	160.9	159.0	69.14	112.75	***
	D3	11	36.1	5.95	0	12	0.90	0.0543	0	8	155.3	154.5	78.53	122.25	**

same magnitude in the control group as in the retinopathy groups

The blood sugar values were higher in the retinopathy groups than in the control group The differences within the diabetic groups were not significant On the other hand the differences between the control group and the retinopathy groups were significant at various levels (see Table XVII)

F Standard bicarbonate and pH at rest and during exercise

I Controls

The mean values in the different age groups 15—24, 25—34 and 35—44 years were approximately the same and are therefore not given separately The values for the combined group 15—44 years are shown in Table XVIII

II a Diabetic subjects grouped according to duration of disease

Table XVIII shows the values in the control group and in the diabetic groups D1, D2 and D 3

Group D3 had the highest pH value at rest the difference being probably significant Otherwise there were no significant differences

As regards the a—v difference, this was about the same in the control group and in D1 without significant differences In groups D2 and D3 the a—v differences were higher, especially during work The group D2 had a significantly higher a—v difference at rest as well as during exercise, while D3 had a significantly higher value only during exercise

The situation was similar when the comparison was made within the diabetic groups However, the only probably significant difference was at rest between groups D1 and D2

II b Diabetic subjects grouped according to retinopathy

Table XV shows the values in the control group and in the retinopathy groups 0, + and ++

The oxygen uptake values were about the same in the control group and in the retinopathy groups The statistical comparison showed only one probably significant difference, namely at rest with a higher value in the group +

There were no significant differences between the retinopathy groups

As regards the a—v difference, no statistical comparison has been made between any of the groups However, with increasing degree of retinopathy the a—v difference became somewhat higher, especially during work

E. Ventilation, respiratory quotient and blood sugar at rest and during exercise

I Controls

The mean values in the different age groups 15—24, 25—34 and 35—44 years were approximately the same and are therefore not given separately The values for the combined group 15—44 years are shown in Table XVI

II a Diabetic subjects grouped according to duration of disease

Table XVI shows the values in the control group and in the diabetic groups D1, D2 and D3

The ventilation values and the respiratory quotients were about the same in the control group and in the diabetic groups at rest as well as during exercise The statistical comparison showed that there was only one probably significant difference, i e the group D3 at rest had a higher ventilation value

The blood sugar values were, of course, higher in the diabetic groups Table XVI gives the levels of significance In group D1 there were only three observations, for which reason a statistical comparison has not been carried out There was no relationship between the blood sugar level and the cardiac output or between the former and the systolic blood pressure Fig 2 shows these relationships at 300 kpm/min

Within the diabetic groups the differences were not significant

II b Diabetic subjects grouped according to retinopathy

Table XVII shows the values in the control group and in the retinopathy groups 0, + and ++

The ventilation values and the respiratory quotients were of about the

Table XVI

Observations in combined control group and in diabetic subjects grouped according to duration of disease Mean values standard deviations and significances for differences from control group are given for ventilation respiratory quotient and blood sugar at rest and at different work loads In addition medians and interquartile ranges ($Q_3—Q_1$) for blood sugar values are given

		Ventilation (l/min)				RQ				Blood sugar (mg 100ml)					
		n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr	n	Mean	Median	S D	Q_3 Q_1	Significance for diff from contr
Rest	Controls	31	7.2	1 37	—	31	0.79	0 0659	—	14	74 5	76 5	21 40	22 00	—
	D1	7	7 4	0 765	0	7	0 79	0 0586	0	3	145 0	139 0	74 18	—	—
	D2	17	8 1	1 76	0	17	0 81	0 0759	0	8	187 0	189 5	61 78	92 75	***
	D3	15	8 2	1 67	*	16	0 80	0 0608	0	10	194 7	197 5	80 99	118 00	***
300 kpm min	Controls	30	20 4	2 90	—	30	0 83	0 0507	—	13	75.0	77 0	8 12	9.50	—
	D1	7	21 3	2 14	0	7	0 84	0.0300	0	3	134 7	122 0	70 85	—	—
	D2	17	19 2	2 62	0	17	0 83	0 0551	0	8	173 4	173.5	64 73	100 00	* *
	D3	14	20 8	4.28	0	15	0 83	0 0484	0	10	179 4	176 5	78.28	114 00	*
600 kpm/min	Controls	24	35 4	6 44	—	24	0 93	0 0614	—	13	75 4	76 0	8 12	11 00	—
	D1	8	37 3	6 08	0	8	0 94	0 0778	0	3	125.7	96 0	68 50	—	—
	D2	13	35 8	4 97	0	13	0 91	0 0743	0	8	160 9	159 0	69 14	112.75	***
	D3	11	36 1	5 95	0	12	0 90	0 0545	0	8	155 3	154.5	78.53	122.2	

same magnitude in the control group as in the retinopathy groups

The blood sugar values were higher in the retinopathy groups than in the control group The differences within the diabetic groups were not significant On the other hand the differences between the control group and the retinopathy groups were significant at various levels (see Table XVII)

E Standard bicarbonate and pH at rest and during exercise

I Controls

The mean values in the different age groups 15—24 25—34 and 35—44 years were approximately the same and are therefore not given separately The values for the combined group 15—44 years, are shown in Table XVIII

II a Diabetic subjects grouped according to duration of disease

Table XVIII shows the values in the control group and in the diabetic groups D1, D2 and D 3

Group D3 had the highest pH value at rest the difference being probably significant Otherwise there were no significant differences

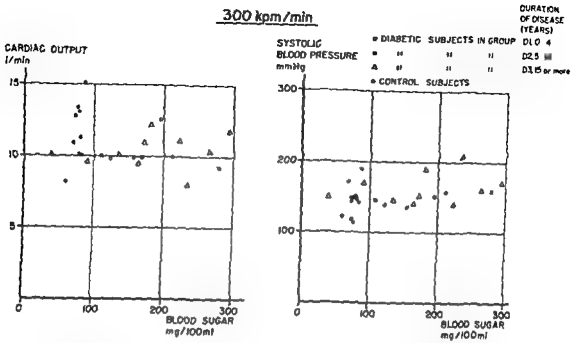

Fig 2 Cardiac output and systolic blood pressure in relationship to the blood sugar value at 300 kpm/min in diabetic subjects grouped according to duration of disease and in the control subjects

Table XVII

Observations in combined control group and in diabetic subjects grouped according to retinopathy. Mean values and standard deviations for ventilation, respiratory quotient and blood sugar, at rest and at different work loads are given. In addition medians, interquartile ranges (Q_3—Q_1) and significances for differences from control group are given for blood sugar values

		Ventilation (l/min)			RQ			Blood sugar (mg/100 ml)					
		n	Mean	S D	n	Mean	S D	n	Mean	Median	S D	Q_3 Q_1	Significance for diff from contr
Rest	Controls	31	7.2	1.37	31	0.79	0.0659	14	74.5	76.5	21.40	22.00	—
	0	11	7.7	1.17	11	0.81	0.0724	7	154.3	117.0	80.26	112.00	***
	+	9	8.9	1.54	9	0.80	0.0550	6	168.3	187.0	68.70	87.00	**
	++	16	7.9	1.75	17	0.81	0.0733	7	220.4	215.0	57.20	116.00	*
300 kpm/min	Controls	30	20.4	2.93	30	0.83	0.0507	13	75.0	77.0	8.12	9.50	—
	0	11	20.0	2.49	11	0.84	0.0617	7	136.4	109.0	78.85	138.00	
	+	9	19.2	2.99	9	0.81	0.0492	6	160.3	175.5	63.62	75.75	
	++	15	20.3	2.64	16	0.83	0.0608	7	204.9	181.0	58.66	100.00	*
600 kpm/min	Controls	24	35.4	6.44	24	0.93	0.0614	13	75.4	76.0	8.12	11.00	—
	0	12	36.1	4.61	12	0.94	0.0718	7	126.0	89.0	80.93	127.00	*
	+	8	34.3	4.59	8	0.88	0.0470	6	146.3	164.0	56.37	78.50	
	++	11	37.3	6.73	12	0.91	0.0709	5	185.2	150.0	68.15	120.0	***

Table XVIII

Observations in combined control group and in diabetic subjects grouped according to duration of disease Mean values, standard deviations and significances for differences from control group are given for arterial carbon dioxide tension, standard bicarbonate and pH, at rest and at different work loads

		Art CO tension (mm Hg)				Stand bicarb (mE/l)				pH			
		n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr
Rest	Controls	23	39.9	5.43	—	[illegible]	23.9	1.34	—	23	7.401	0.0278	—
	D1	8	41.2	2.60	0	8	24.9	1.96	0	[illegible]	7.409	0.0312	[illegible]
	D2	17	38.7	3.53	0	17	24.0	1.20	0	17	7.413	0.0315	[illegible]
	D3	15	36.3	6.01	[illegible]	15	24.4	2.22	0	15	7.435	0.0513	[illegible]
300 kpm/min	Controls	23	42.6	3.38	—	23	23.2	0.864	—	23	7.371	0.0169	—
	D1	8	39.6	3.92	*	8	23.5	1.79	[illegible]	8	7.394	0.0411	0
	D2	17	41.7	4.74	0	17	22.7	1.20	0	17	7.371	0.0208	0
	D3	15	39.9	4.74		15	23.0	2.18	[illegible]	15	7.382	0.0340	[illegible]
600 kpm/min	Controls	21	43.3	3.17	—	21	22.2	1.12	—	21	7.350	0.0231	—
	D1	7	38.7	3.65	**	7	21.5	1.50	0	7	7.369	0.0293	0
	D2	14	40.9	4.51	*	13	21.4	1.93	0	14	7.349	0.0340	0
	D3	12	40.5	5.31	*	12	21.8	2.20	0	12	7.357	0.0400	0

II b Diabetic subjects grouped according to retinopathy

Table XIX shows the values in the control group and in the retinopathy groups 0 + and ++

The pH values were approximately the same in the different groups with a tendency to lower values in the control group The standard bicarbonate was about the same in the control group as in the retinopathy groups No statistical comparison has been performed

G Haematocrit value and haemoglobin concentration at rest and during exercise

I Controls

The mean values in the different age groups 15—24, 25—34 and 35—44 years were approximately the same and are therefore not given separately The values for the combined group, 15—44 years are shown in Table XX

II a Diabetic subjects grouped according to duration of disease

Table XX shows the values in the control group and in the diabetic groups D1 D2 and D3

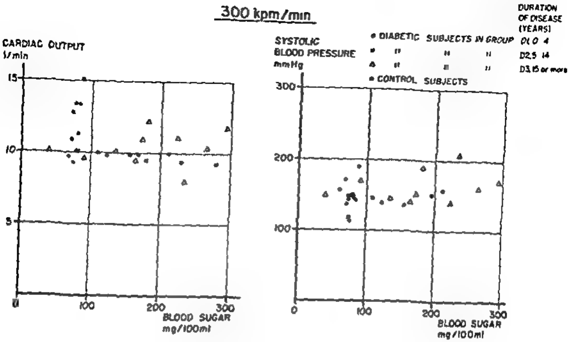

Fig 2 Cardiac output and systolic blood pressure in relationship to the blood sugar value at 300 kpm/min in diabetic subjects grouped according to duration of disease and in the control subjects

Table XVII

Observations in combined control group and in diabetic subjects grouped according to retinopathy Mean values and standard deviations for ventilation, respiratory quotient and blood sugar, at rest and at different work loads are given In addition medians, interquartile ranges (Q_3—Q_1) and significances for differences from control group are given for blood sugar values

		Ventilation (l/min)			RQ			Blood sugar (mg/100 ml)					
		n	Mean	SD	n	Mean	SD	n	Mean	Median	SD	Q_3 Q_1	Significance for diff from contr
Rest	Controls	31	7.2	1.37	31	0.79	0.0659	14	74.5	76.5	21.40	22.00	—
	0	11	7.7	1.17	11	0.81	0.0724	7	154.3	117.0	80.26	112.00	***
	+	9	8.9	1.54	9	0.80	0.0550	6	168.3	187.0	68.70	87.00	**
	++	16	7.9	1.75	17	0.81	0.0733	7	220.4	215.0	57.20	116.00	**
300 kpm/min	Controls	30	20.4	2.90	30	0.83	0.0507	13	75.0	77.0	8.12	9.50	—
	0	11	20.0	2.49	11	0.84	0.0617	7	136.4	109.0	78.85	138.00	
	+	9	19.2	2.99	9	0.61	0.0492	6	160.3	175.5	63.62	75.75	
	++	15	20.3	2.64	16	0.83	0.0608	7	204.9	181.0	58.66	100.00	**
600 kpm/min	Controls	24	35.4	6.44	24	0.93	0.0614	13	75.4	76.0	8.12	11.00	—
	0	12	36.1	4.61	12	0.94	0.0718	7	126.0	89.0	80.93	127.00	
	+	8	34.3	4.59	8	0.88	0.0470	6	146.3	164.0	56.37	78.50	*
	++	11	37.3	6.73	12	0.91	0.0709	5	185.2	150.0	68.15	120.0	***

Table XX

Observations in combined control group and in diabetic subjects grouped according to duration of disease Mean values, standard deviations and significances for differences from control group are given for haematocrit value, haemoglobin concentration and arterial oxygen saturation, at rest and at different work loads

		Haematocrit value (%)				Haemoglobin conc (g/100 ml)				Art O_2 saturation (%)			
		n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr	n	Mean	S D	Significance for diff from contr
Rest	Controls	31	41.4	3.15	—	29	13.9	1.34	—	29	97.1	2.15	—
	D1	7	43.9	1.35	+	8	14.0	0.700	0	8	95.8	2.12	0
	D2	17	43.5	2.87	+	17	14.7	1.29	0	17	96.4	2.20	0
	D3	16	42.8	2.67	[illegible]	16	14.4	0.968	0	15	97.4	2.81	0
300 kpm/min	Controls	31	42.[illegible]	2.80	—	30	14.2	1.22	—	28	96.3	1.95	—
	D1	7	43.7	1.60	0	8	14.6	0.711	0	8	95.8	2.45	0
	D2	17	44.9	2.85	+	17	15.1	1.23		17	94.8	2.70	0
	D3	16	43.6	2.73	0	16	14.7	0.905	0	15	96.5	3.77	0
600 kpm/min	Controls	25	43.6	3.21	—	25	14.3	1.31	—	25	95.8	2.20	—
	D1	6	44.7	2.58	0	7	14.8	1.06	[illegible]	7	96.6	3.55	0
	D2	14	46.6	3.32	+	14	15.4	1.12	+	14	95.5	3.07	0
	D3	13	45.7	2.93	0	13	15.3	0.753	+	12	95.6	3.80	0

The arterial carbon dioxide tension at rest was lowest in the group D3 The difference was not significant However, during exercise the values were significantly lower in the diabetic groups For information of the levels of significance see Table XVIII

The oxygen saturation was about the same in the control group as in the diabetic groups, the differences being not significant

A statistical comparison within the diabetic groups showed that at 300 kpm/min the oxygen saturation in group D3 was probably significantly higher than in the group D2

II b Diabetic subjects grouped according to retinopathy

Tables XIX and XXI show the values in the control group and in the different retinopathy groups 0, + and ++

I Comparison between indirectly measured systolic blood pressure during exercise in the sitting position and intra arterially measured systolic blood pressure during exercise in the supine position

From a practical clinical point of view it would be of interest to know

Table XIX

Observations in combined control group and in diabetic subjects grouped according to retinopathy *Mean values and standard deviations* are given for arterial carbon dioxide tension, standard bicarbonate and pH, at rest and at different work loads

		Art CO tension (mm Hg)			Stand bicarb (mE/l)			pH		
		n	Mean	S D	n	Mean	S D	n	Mean	S D
Rest	Controls	23	39 9	5 43	23	23 9	1 34	23	7 401	0 0278
	0	12	39 3	4 01	12	24 0	1 41	12	7 407	0 0316
	+	8	38 0	5 37	8	24 3	1 89	8	7 423	0 0501
	++	17	38 1	5 03	17	24 9	1 73	17	7 434	0 0398
300 kpm/min	Controls	23	42 6	3 38	23	23 2	0 864	23	7 371	0 0169
	0	12	40 9	4 05	12	23 0	1 20	12	7 378	0 0293
	+	8	39 8	5 01	8	22 6	1 41	8	7 378	0 0154
	++	17	41 4	4 87	17	23 6	1 59	17	7 389	0 0342
600 kpm/min	Controls	21	43 3	3 17	21	22 2	1 12	21	7 350	0 0231
	0	12	38 8	3 66	12	21 2	1 95	12	7 358	0 0350
	+	7	40 4	4 03	7	22 4	0 802	7	7 368	0 0211
	++	13	41 9	5 49	12	21 8	2 07	13	7 353	0 0399

It will immediately be seen from the table that the haematocrit value as well as the haemoglobin concentration were lower in the control group than in the diabetic groups A plausible explanation for this is that there were seven blood donors in the control group The mean haemoglobin concentration in these seven subjects was 12 8 g/100 ml as compared with 14 2 g/100 ml in the remaining 22 control subjects, where information was available This latter value was approximately the same as in the diabetic groups

II b Diabetic subjects grouped according to retinopathy

Table XXI shows the values in the control group and in the retinopathy groups 0, + and ++

With this grouping, also, the diabetic subjects had higher values for haematocrit and haemoglobin concentration

H Carbon dioxide tension and arterial oxygen saturation at rest and during exercise

I Controls

The mean values in the different age groups 15—24, 25—34 and 35—44 years were approximately the same and are therefore not given separately The values for the combined group, 15—44 years, are shown in Tables XVIII and XX

II a Diabetic subjects grouped according to duration of disease

Tables XVIII and XX show the values in the control group and in the diabetic groups D1, D2 and D3

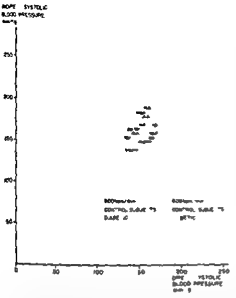

Fig 3 Comparison of indirect measurements of systolic blood pressure during an ordinary exercise test in the sitting position with direct measurements during exercise in the supine position

essentially normal at rest but definitely lower during exercise Cardiac output is governed by heart rate and stroke volume In the present series there were no clear cut differences in heart rate and it has therefore been judged that a lower stroke volume was the decisive factor for the reduction of cardiac output

Several factors may explain the lower stroke volume in the diabetic subjects but at present no definite answer can be given This is in part dependent upon the complexity of the factors which influence the stroke volume in man In the groups with 5—14 and 15 or more years duration of diabetes the stroke volumes were lower even at rest The same held for the group with a moderate degree of retinopathy Since heart rates were about the same it is not likely that the lower stroke volumes in these diabetic groups was due to a more basal condition It is well known that the stroke volume may be increased by an emotional stimulant and arterial catheterization is one such stimulus However, the fact that stroke volumes in diabetics were also lower during exercise indicated that a emotional tension is not a decisive factor in this complex

The stroke volume is dependent upon the size of the cardiac muscle An expression for the heart size can be obtained in the diabetic subjects whose heart volumes were known The average heart volume in all diabetic groups was between 380 and 390 ml/m² body surface area Heart volumes were not measured in the control group but it seems rather unlikely that it would have been much different from that in the group of diabetics with the shortest duration of disease It cannot be excluded entirely that a certain degree of physical inactivity with reduction in stroke volume and heart volume may be a factor which at least in part could explain the differences from the controls in this respect It was indeed found that the diabetic patients had a slightly lower physical working capacity although the differences were rather small (17)

The degree of physical fitness is of importance for the stroke volume since it is known that this will increase under physical training and is larger in well trained athletes see for examp-

Table XXI

Observations in combined control group and in diabetic subjects grouped according to retinopathy Mean values and standard deviations are given for haematocrit value, haemoglobin concentration and arterial oxygen saturation, at rest and at different work loads

		Haematocrit value (%)			Haemoglobin conc (g/100 ml)			Art O saturation (%)		
		n	Mean	SD	n	Mean	SD	n	Mean	SD
Rest	Controls	31	41.4	3.15	29	13.9	1.34	29	97.1	2.15
	0	11	44.0	2.24	12	14.3	1.03	12	95.9	1.94
	+	9	44.2	2.28	9	15.0	0.615	8	95.4	3.20
	++	17	42.4	2.74	17	14.3	1.16	17	97.8	2.21
300 kpm/min	Controls	31	42.9	2.80	30	14.2	1.22	28	96.3	1.95
	0	11	44.3	3.00	12	14.8	1.01	12	95.8	3.07
	+	9	45.3	1.94	9	15.2	0.853	8	96.1	1.45
	++	17	43.6	2.50	17	14.8	1.03	17	95.4	3.74
600 kpm/min	Controls	25	43.6	3.21	25	14.3	1.31	25	95.8	2.20
	0	11	45.7	3.52	12	15.1	1.30	12	95.9	3.53
	+	8	46.5	2.88	8	15.3	0.725	7	96.2	3.47
	++	13	45.3	2.72	13	15.4	0.849	13	95.4	3.50

whether the systolic blood pressure, measured by the auscultatory method during an ordinary exercise test, agrees satisfactorily with the intra-arterial systolic blood pressure measured during a more elaborate haemodynamic investigation involving exercise in the supine position For that reason the systolic blood pressures obtained in the two types of examination are shown graphically in Fig 3, the values from a previous (17) and the present study being used It should be noted that the exercise test in the sitting position and the haemodynamic investigation were not always carried out in close time succession with one another Consequently, diabetic patients have been excluded when the time interval exceeded eight months and/or when the diabetic subject would have had to be placed in a different duration or retinopathy group After this, 33 diabetic patients and 13 controls remained

The figure shows a reasonable agreement between the findings on the two occasions The results obtained in the present study thus confirm the results obtained from an ordinary simple exercise test (17)

DISCUSSION

In comparison with a control group, all groups of diabetic patients, whether the division was made according to duration of disease or to retinopathy showed a cardiac output which was

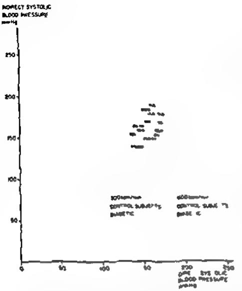

Fig 3 Comparison of indirect measurements of systolic blood pressure during an ordinary exercise test in the sitting position with direct measurements during exercise in the supine position

essentially normal at rest but definitely lower during exercise Cardiac output is governed by heart rate and stroke volume In the present series there were no clear cut differences in heart rate and it has therefore been judged that a lower stroke volume was the decisive factor for the reduction of cardiac output

Several factors may explain the lower stroke volume in the diabetic subjects but at present no definite answer can be given This is in part dependent upon the complexity of the factors which influence the stroke volume in man In the groups with 5—14 and 15 or more years duration of diabetes the stroke volumes were lower even at rest The same held for the group with a moderate degree of retinopathy Since heart rates were about the same it is not likely that the lower stroke volumes in these diabetic groups was due to a more basal condition It is well known that the stroke volume may be increased by an emotional stimulant and arterial catheterization is one such stimulus However, the fact that stroke volumes in diabetics were also lower during exercise indicated that a emotional tension is not a decisive factor in this complex

The stroke volume is dependent upon the size of the cardiac muscle An expression for the heart size can be obtained in the diabetic subjects whose heart volumes were known The average heart volume in all diabetic groups was between 380 and 390 ml/m² body surface area Heart volumes were not measured in the control group but it seems rather unlikely that it would have been much different from that in the group of diabetics with the shortest duration of disease It cannot be excluded entirely that a certain degree of physical inactivity, with reduction in stroke volume and heart volume may be a factor, which at least in part could explain the differences from the controls in this respect It was indeed found that the diabetic patients had a slightly lower physical working capacity although the differences were rather small (17)

The degree of physical fitness is of importance for the stroke volume since it is known that this will increase under physical training and is larger in well trained athletes, see for examp

le Åstrand, 1956 and Bevegård, 1962 (1, 5)

The behaviour of the stroke volume during muscular exercise is dependent also upon body posture. During sitting exercise cardiac output and stroke volumes are lower than when the exercise is performed in the supine position (6). In the present study, both controls and diabetics were examined in the supine position at rest and during exercise. In the control group the increase in stroke volume from rest to the work load 600 kpm/min was 17 per cent of the resting value, which is in reasonable agreement with the 10—20 per cent reported by for example Grimby 1962 (12). The corresponding increase in the diabetic groups was slightly lower, 5—13 per cent but apparently the difference in this respect both in controls and diabetics was not particularly large, if any. The maximal stroke volume in sitting exercise is already reached at an oxygen uptake of about 40 per cent of the maximal and at a heart rate of about 110/min (2). It is therefore reasonable to assume that both controls and diabetics reached values for the stroke volume which were maximal at the highest work load, particularly when it is known that the stroke volume is higher during recumbent exercise.

An important possibility to be considered is whether the smaller stroke volumes in diabetic patients may be due to disturbances in myocardial metabolism. This has been studied in later years in healthy subjects as well as in diabetics (e.g. 7, 8, 23). It was found that diabetics differed from healthy individuals in the respect that insulin administration raised the relative myocardial uptake of linoleic acid whereas it was lowered in most non-diabetic controls (8, 23). However, at present it is not possible to evaluate the relationship between myocardial metabolism and myocardial function, although it would seem possible that, at least in poorly controlled diabetics, such metabolic differences might be of importance. It seems relatively unlikely that the present group of diabetics who were reasonably well regulated and who had a normal skeletal muscle function, differed radically from the controls as regards myocardial metabolism.

Reduction of myocardial blood flow due to coronary arteriosclerosis leads to a reduction in myocardial performance (9, 18, 20). Since changes in the coronary arteries occur early in diabetic subjects (e.g. 15), it seems fully possible that a reduced myocardial blood flow could be a contributing factor to the lower stroke volumes. However, nothing is known about myocardial function in patients with coronary insufficiency of lesser degree. In this connection it may be mentioned that the present diabetic series has a high frequency of electrocardiographic changes (16). At present it does not seem possible to evaluate the relationship between electrocardiographic changes, coronary arteriosclerosis and myocardial performance in diabetic subjects due to the relatively limited material. It is hoped that subsequent observations in the same patients will reveal whether

coronary arteriosclerosis is of importance

In a discussion of the other haemodynamic results of interest i e the intra arterial pressures and the calculated peripheral vascular resistance, it must first be pointed out that, as regards arterial pressure there were no differences between the controls and the group of diabetics with the shortest duration of disease, this was in good argreement with previous results obtained by auscultatory measurement of the blood pressure at rest and during sitting exercise (17) In spite of lower cardiac output, the calculated vascular resistance was not significantly different from the control group in these patients either Secondly, there were no certain differences in arterial pressure between the control group and the groups without or with a mild form of retinopathy while on the other hand the calculated vascular resistance was definitely higher in these diabetic groups since their cardiac output was lower Thirdly, the results of these direct measurements of arterial pressure supported the indirect observations previously reported (17) It could be confirmed that the increase in systolic arterial blood pressure became significantly higher only during exercise in the groups with a duration of 5—14 years of diabetes or with a moderate form of retinopathy As previously observed (17) it should be pointed out that in groups with a longer duration of disease and with a moderate form of retinopathy, raised blood pressures were present even at rest

The intra arterial pressure measurements revealed that the systolic the diastolic and the mean arterial pressures were raised both at rest and during exercise This suggests that a reduction of the elasticity of the larger arteries cannot be the only cause of the hypertension in diabetics during exercise An increase in the peripheral vascular resistance must have existed, but, as previously mentioned (17), it cannot be said whether this is due to functional and/or organic changes

The increased peripheral vascular resistance in groups with increased mean arterial pressures and lowered cardiac output follows from the definition of vascular resistance used It is of course, possible that this increased resistance is caused by changes in the peripheral vascular bed However, the cardiac output is not always lowered concurrently with high peripheral vascular resistance This was shown by for example Varnauskas, 1955 (24), in patients with essential hypertension The raised calculated vascular resistance during exercise in groups in which the arterial pressure was not significantly abnormal, for example retinopathy groups 0 and +, was due to lowered cardiac output These observations may be interpreted in various ways but it would seem possible that, early in the history of the disease, there is a lowered cardiac output due to a lowered stroke volume and that later on vascular changes develop and that these factors together increase the calculated vascular resistance

In a previous article (17) it was

demonstrated by observations before, and 30 minutes after the exercise test, that diabetic patients treated with insulin had a larger fall in blood glucose than the controls. In this connection it was discussed whether a release of adrenaline could occur in the diabetic patients and influence the haemodynamic situation. However, this was regarded as unlikely. Also, in the present study, where during exercise blood glucose fell significantly in diabetic subjects but was unchanged in the controls, it may be questioned whether adrenaline was of any importance. Adrenaline will increase cardiac output and lower vascular resistance (3, 27). However, since all diabetic subjects had a low cardiac output during exercise, and since all except those with the shortest duration of disease had increased peripheral vascular resistance, it seems quite unreasonable that an increased release of adrenaline in the diabetic patient could be the cause of the haemodynamic differences observed.

In most other respects, e.g. pulmonary ventilation, oxygen uptake, respiratory quotient, acid-base balance and blood oxygen saturation, controls and diabetics were similar. Haemoglobin and haematocrit values were slightly lower in the controls, but on the other hand there were no differences among the diabetics. The reason why the haemoglobin and haematocrit values were slightly lower may be the fact that seven of the controls were blood donors. However, they did not differ from the remaining controls as regards cardiac output, stroke volume and blood pressures at rest and during exercise. Consequently, the small difference in the haemoglobin concentration between the control group and the diabetic groups cannot explain the haemodynamic differences.

The arterial carbon dioxide tension during exercise was lower in the diabetics, on the other hand there were no differences in pH and standard bicarbonate between controls and diabetics. No explanation can be given for this difference. It should be emphasized that there were no signs of acidosis at rest or during exercise in the diabetic subjects, as compared with the controls.

SUMMARY

Forty-one male diabetics, aged 18—44 years, and a control group of thirty-one healthy males, aged 19—44 years, were examined with determinations of *inter alia* the intra-arterial pressures, cardiac output, oxygen uptake, arterial carbon dioxide tension, standard bicarbonate, pH and blood sugar at rest and during graded physical exercise in the supine position. The diabetic subjects were grouped according to duration of disease, 0—4, 5—14 and 15 or more years, and according to the degree of retinopathy, corresponding to absence and presence of mild or moderate retinopathy.

All diabetic groups showed a lower cardiac output during exercise without significant differences at rest. This was due to a lower stroke volume.

The group with 0—4 years duration of disease and the groups without

or with a mild form of retinopathy were not different from the controls as regards intra-arterial blood pressures at rest or during exercise The groups with 5—14 years duration of disease and with a moderate form of retinopathy were not different from the controls as regards the systolic arterial pressure at rest but had a higher systolic pressure during exercise The diastolic blood pressure and the mean arterial pressure in these groups was higher both at rest and during exercise The group with a duration of the disease of 15 or more years had higher arterial pressures than the controls both at rest and during exercise

The group with 0—4 years duration of disease was not significantly different either at rest or during exercise from the controls as regards the peripheral vascular resistance Patients with a longer duration of disease had higher calculated vascular resistance both at rest and during exercise The groups without or with a mild form of retinopathy had a higher calculated vascular resistance during exercise, whereas the group with a moderate form of retinopathy already had this at rest

Blood glucose values were higher in the diabetic patients and fell during exercise, in contrast to the blood glucose in the controls, which was unchanged Otherwise there were no signs of a different metabolism in the diabetic patients

The results were discussed with regard to possible explanations and their occurrence during the course of the diabetic disease

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demonstrated by observations before, and 30 minutes after the exercise test, that diabetic patients treated with insulin had a larger fall in blood glucose than the controls In this connection it was discussed whether a release of adrenaline could occur in the diabetic patients and influence the haemodynamic situation However, this was regarded as unlikely Also, in the present study, where during exercise blood glucose fell significantly in diabetic subjects but was unchanged in the controls, it may be questioned whether adrenaline was of any importance Adrenaline will increase cardiac output and lower vascular resistance (3, 27) However, since all diabetic subjects had a low cardiac output during exercise, and since all except those with the shortest duration of disease had increased peripheral vascular resistance, it seems quite unreasonable that an increased release of adrenaline in the diabetic patient could be the cause of the haemodynamic differences observed

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SUMMARY

Forty-one male diabetics, aged 18—44 years, and a control group of thirty-one healthy males, aged 19—44 years, were examined with determinations of *inter alia* the intra-arterial pressures, cardiac output, oxygen uptake, arterial carbon dioxide tension, standard bicarbonate, pH and blood sugar at rest and during graded physical exercise in the supine position The diabetic subjects were grouped according to duration of disease, 0—4, 5—14 and 15 or more years, and according to the degree of retinopathy, corresponding to absence and presence of mild or moderate retinopathy

All diabetic groups showed a lower cardiac output during exercise without significant differences at rest This was due to a lower stroke volume

The group with 0—4 years duration of disease and the groups without

Table V (continued)

Case No		Heart rate (beats/min)	Cardiac output (l/min)	Stroke volume (ml)	Pressure in brachial artery (mm Hg) Syst	Diast	Mean	Oxygen uptake (ml/min)
D 23	Rest	68	—	—	121	[illegible]	87	295
	300	115	—	—	142	[illegible]	104	—
	600	142	—	—	156	[illegible]	107	1540
D 24	Rest	55	5.5	100	165	88	110	284
	300	92	10.5	114	183	[illegible]	125	1038
	600	126	12.6	100	232	113	159	1702
D 26	Rest	81	6.2	77	120	72	92	298
	300	105	9.4	90	155	83	112	885
	600	130	12.6	97	192	93	125	—
D 27	Rest	75	7.5	100	140	70	100	357
	300	96	12.2	127	190	90	130	1071
	700	127	13.6	107	238	97	160	1795
D 29	Rest	63	6.0	95	132	77	101	239
	300	91	11.9	131	129	70	94	928
	600	112	12.5	112	157	80	112	1310
D 30	Rest	89	7.0	79	126	77	97	313
	300	110	11.4	104	166	85	113	877
	600	145	13.3	92	194	102	134	1974
D 31	Rest	60	4.2	70	128	79	94	263
	300	98	8.9	91	168	81	108	1055
	600	—	—	—	—	—	—	—
D 32	Rest	76	7.7	101	122	67	87	257
	300	120	12.2	102	150	75	99	—
	600	145	14.8	102	170	75	109	—
D 40	Rest	68	8.0	118	122	65	[illegible]	283
	300	120	15.5	129	140	60	90	953
	600	160	18.5	116	164	76	109	1480
D 44	Rest	54	5.5	102	127	76	91	305
	300	[illegible]	10.0	114	146	87	114	740
	600	116	14.5	125	194	102	137	1706
D 46	Rest	70	6.9	99	106	61	[illegible]	307
	300	97	9.9	102	115	61	86	876
	600	121	13.7	113	128	67	94	1338
D 50	Rest	52	4.7	90	140	76	100	237
	300	93	11.1	119	164	78	113	1058
	600	125	—	—	188	82	114	—
D 52	Rest	67	7.6	113	118	69	85	252
	300	105	12.8	122	118	73	90	904
	600	132	15.1	114	137	77	97	1415
D 54	Rest	72	8.4	117	119	72	91	314
	300	94	9.5	101	134	75	93	911
	600	120	12.0	100	150	78	103	1537

Table V

Observations in individual diabetic subjects at rest and at various work loads (300 and 600 kpm/min)

Case No		Heart rate (beats/min)	Cardiac output (l/min)	Stroke volume (ml)	Pressure in brachial artery (mm Hg) Syst	Diast	Mean	Oxygen uptake (ml/min)
D 2	Rest	67	5.2	78	113	73	94	264
	300	103	9.7	94	169	90	124	921
	600	146	14.4	99	196	103	137	1439
D 3	Rest	64	4.9	77	146	88	113	283
	300	114	8.7	76	194	116	154	926
	600	155[1]	11.1	72	214	125	166	1325
D 4	Rest	61	5.4	89	120	68	89	286
	300	83	10.1	122	146	77	106	938
	600	112	15.3	137	186	90	129	1569
D 6	Rest	79	7.2	91	125	64	89	348
	300	115	13.4	117	159	83	108	1043
	600	150	17.2	115	182	92	121	1702
D 11	Rest	80	9.5	119	134	68	92	377
	300	98	12.6	129	151	72	106	914
	600	120	14.7	123	178	79	115	1489
D 12	Rest	65	6.9	106	117	70	88	216
	300	101	9.5	94	141	81	105	876
	600	134	16.0	119	182	93	123	1598
D 14	Rest	49	4.6	94	119	65	91	301
	300	86	7.2	84	146	79	103	830
	600	109	12.0	110	183	94	127	1315
D 15	Rest	72	5.9	82	114	69	94	282
	300	98	9.8	100	147	83	118	1121
	600	121	10.7	88	155	82	111	1282
D 16	Rest	102	7.6	75	144	83	110	334
	300	130	11.4	88	210	101	135	889
	600	152	14.3	94	211	86	135	1146
D 18	Rest	102	7.4	73	174	96	132	315
	300	127	9.4	74	199	91	133	1088
	600	—	—	—	—	—	—	—
D 19	Rest	90	4.5	50	137	91	114	258
	300	121	9.2	76	183	100	134	943
	600	161	10.8	67	194	103	143	1597
D 21	Rest	83	9.0	108	115	69	89	294
	300	115	11.8	103	154	69	103	1019
	600	162	—	—	195	88	129	1925
D 22	Rest	59	8.1	137	122	78	98	346
	300	87	10.0	115	136	79	102	847
	600	108	12.1	112	149	81	108	1480

[1]) Not in steady state

Table V (continued)

Case No		Heart rate (beats/min)	Cardiac output (l/min)	Stroke volume (ml)	Pressure in brachial artery (mm Hg) Syst	Diast	Mean	Oxygen uptake (ml/min)
D 23	Rest	68	—	—	121	68	87	295
	300	115	—	—	142	78	104	—
	600	142	—	—	156	83	107	1540
D 24	Rest	55	5.5	100	165	[illegible]	110	284
	300	92	10.5	114	183	86	125	1038
	600	126	12.6	100	232	113	159	1702
D 26	Rest	81	6.2	77	120	72	92	298
	300	105	9.4	90	155	83	112	885
	600	130	12.6	97	192	93	125	—
D 27	Rest	75	7.5	100	140	70	100	357
	300	96	12.2	127	190	90	130	1071
	700	127	13.6	107	238	97	160	1795
D 29	Rest	63	6.0	95	132	77	101	239
	300	91	11.9	131	129	70	94	928
	600	112	12.5	112	157	80	112	1310
D 30	Rest	89	7.0	79	126	77	97	313
	300	110	11.4	104	166	85	113	877
	600	145	13.3	92	194	102	134	1974
D 31	Rest	60	4.2	70	128	79	94	263
	300	98	8.9	91	168	81	108	1055
	600	—	—	—	—	—	—	—
D 32	Rest	76	7.7	101	122	67	87	257
	300	120	12.2	102	150	75	99	—
	600	145	14.8	102	170	75	109	—
D 40	Rest	[illegible]	8.0	118	122	65	[illegible]	283
	300	120	15.5	129	140	60	90	955
	600	160	18.5	116	164	76	109	1480
D 44	Rest	54	5.5	102	127	76	91	305
	300	[illegible]	10.0	114	146	87	114	740
	600	116	14.5	125	194	102	137	1706
D 46	Rest	70	6.9	99	106	61	81	307
	300	97	9.9	102	115	61	86	876
	600	121	13.7	113	128	67	94	1388
D 50	Rest	52	4.7	90	140	76	100	237
	300	93	11.1	119	164	78	113	1058
	600	125	—	—	188	[illegible]	114	—
D 52	Rest	67	7.6	113	118	69	85	252
	300	105	12.8	122	118	73	90	904
	600	132	15.1	114	137	77	97	1415
D 54	Rest	72	8.4	117	119	72	91	314
	300	94	9.5	101	134	75	[illegible]	911
	600	120	12.0	100	150	78	103	1537

Table V (continued)

Case No		Heart rate (beats/min)	Cardiac output (l/min)	Stroke volume (ml)	Pressure in brachial artery (mm Hg) Syst	Diast	Mean	Oxygen uptake (ml/min)
D 56	Rest	64	5.8	91	109	66	87	366
	300	95	9.9	104	132	68	90	903
	600	135	12.8	95	163	83	115	1666
D 59	Rest	85	7.3	86	133	73	95	279
	300	116	11.8	102	172	82	108	976
	600	147	14.3	97	195	89	128	1468
D 61	Rest	81	6.1	75	145	83	113	300
	300	108	8.5	79	146	75	103	888
	600	145	10.8	74	185	97	129	1606
D 66	Rest	76	6.9	91	124	67	88	298
	300	103	10.1	98	149	72	92	729
	600	136	12.0	88	185	86	117	1498
D 68	Rest	60	6.1	102	118	70	93	292
	300	85	9.9	116	136	70	99	832
	600	113	13.8	122	156	74	105	1468
D 70	Rest	69	5.6	81	119	74	93	260
	300	108	10.9	101	136	71	96	944
	600	150	14.9	99	165	83	112	1635
D 74	Rest	63	5.7	90	149	86	111	292
	300	95	9.6	101	170	89	120	1007
	600	130	13.3	102	206	107	146	1744
D 77	Rest	92	8.1	88	133	71	97	—
	300	123	10.0	81	158	73	103	970
	600	150	13.3	89	182	82	113	1386
D 79	Rest	55	6.5	118	121	68	[illegible]	304
	300	86	9.8	114	139	74	99	959
	600	114	12.1	106	160	79	110	1422
D 79	Rest	63	6.6	105	126	74	94	337
	300	86	11.0	128	152	75	102	1096
	600	121	14.9	123	205	92	126	1799
D 80	Rest	54	6.5	120	116	64	84	174
	300	96	11.1	116	140	77	101	996
	600	140	16.7	119	194	93	120	1663
D 81	Rest	74	5.9	80	182	97	134	257
	300	98	8.0	82	209	107	149	625
	600	137	10.0	73	247	123	181	1473
D 83	Rest	83	6.5	78	125	78	102	301
	300	111	9.3	84	160	86	115	763
	600	155	13.6	88	204	99	137	1191
D 85	Rest	84	5.7	68	127	76	96	308
	300	135	10.4	77	161	92	116	787
	600	—	—	—	—	—	—	—

Table VI

Observations in individual diabetic subjects at rest and at various work loads (300 and 600 kpm/min) * = samples not stored at +4° C For further explanation, see text

Case No		Arterial O_2 sat (%)	Arterial CO_2 tension (mm Hg)	pH	Stand bicarb (mE/l)	Haemoglobin conc (g/100 ml)	Haematocrit value (%)	Ventilation (l/min)	RQ	Blood sugar (mg/100 ml)
D 2	Rest	93.8	41.0	7.430	25.0	14.2	45	5.9	0.78	*200
	300	94.5	50.0	7.370	22.0	15.6	46	20.5	0.88	*200
	600	94.2	49.0	7.340	—	15.9	48	35.1	0.95	*180
D 3	Rest	91.5	34.0	7.408	22.0	15.6	45	8.1	0.79	*212
	300	94.3	32.0	7.373	20.0	15.8	46	21.5	0.87	*195
	600	91.8	27.5	7.353	18.0	16.1	48	34.2	1.04	*191
D 4	Rest	99.7	29.0	7.485	24.0	14.0	40	10.5	0.94	149
	300	93.5	41.5	7.355	22.0	13.9	43	17.4	0.76	134
	600	93.2	47.0	7.290	20.0	14.4	45	30.3	0.86	119
D 6	Rest	93.5	38.5	7.425	25.0	16.2	48	6.8	0.77	*200
	300	94.6	45.0	7.380	24.0	16.7	51	18.2	0.78	*190
	600	96.8	42.0	7.350	22.0	17.4	52	31.1	0.82	*180
D 11	Rest	94.8	35.0	7.440	24.0	13.8	41	12.0	0.90	204
	300	95.7	40.0	7.390	23.5	13.4	42	19.4	0.75	195
	600	98.7	41.0	7.373	22.5	14.0	41	36.0	0.87	189
D 12	Rest	97.1	44.0	7.450	28.5	14.2	42	4.7	0.78	215
	300	85.0	46.0	7.390	25.5	15.1	44	15.6	0.82	164
	600	85.6	50.0	7.350	24.5	15.8	46	28.2	0.86	149
D 14	Rest	96.2	40.0	7.410	24.0	15.6	43	8.3	0.84	*108
	300	94.3	36.0	7.365	21.0	15.3	45	16.3	0.80	* 99
	600	95.9	33.0	7.385	21.0	15.5	48	29.3	0.92	* 87
D 15	Rest	98.6	45.0	7.399	25.5	15.6	48	—	0.81	—
	300	101.0	44.0	7.423	27.0	15.6	48	—	0.88	143
	600	97.2	41.0	7.432	26.0	16.7	49	—	0.90	*104
D 16	Rest	92.7	36.5	7.407	23.0	12.9	41	7.7	0.76	*175
	300	99.4	39.0	7.388	23.0	14.0	40	20.6	0.84	*170
	600	99.4	35.0	7.385	21.5	14.2	41	27.1	0.83	*160
D 18	Rest	96.6	30.0	7.445	23.0	12.3	40	9.1	0.76	*407
	300	99.6	36.0	7.320	19.0	12.5	39	31.8	0.87	*419
	600	—	—	—	—	—	—	—	—	—
D 19	Rest	99.6	27.0	7.540	26.0	15.3	42	10.1	0.89	*263
	300	95.8	41.0	7.377	23.[illegible]	15.5	42	20.9	0.82	*240
	600	94.5	34.0	7.370	20.5	15.9	43	38.5	0.89	*225
D 21	Rest	99.0	43.0	7.465	28.5	14.8	43	6.5	0.68	*140
	300	95.5	38.0	7.470	27.0	15.3	44	21.1	0.76	*140
	600	—	—	—	—	—	—	46.7	0.87	*140
D 22	Rest	96.6	42.5	7.405	24.0	15.1	48	7.8	0.79	*121
	300	97.5	43.0	7.390	23.0	15.6	48	16.2	0.79	*2[illegible]0
	600	100.0	4[illegible].0	7.380	23.0	15.6	49	30.5	0.86	*180

Table V (continued)

Case No		Heart rate (beats/min)	Cardiac output (l/min)	Stroke volume (ml)	Pressure in brachial artery (mm Hg) Syst	Diast	Mean	Oxygen uptake (ml/min)
D 56	Rest	64	5.8	91	109	66	87	366
	300	95	9.9	104	132	68	90	903
	600	135	12.8	95	163	83	115	1666
D 59	Rest	85	7.3	86	133	73	95	279
	300	116	11.8	102	172	82	108	976
	600	147	14.3	97	195	89	128	1468
D 61	Rest	81	6.1	75	145	83	113	300
	300	108	8.5	79	146	75	103	888
	600	145	10.8	74	185	97	129	1606
D 66	Rest	76	6.9	91	124	67	88	298
	300	103	10.1	98	149	72	92	729
	600	136	12.0	88	185	86	117	1498
D 68	Rest	60	6.1	102	118	70	93	292
	300	85	9.9	116	136	70	99	832
	600	113	13.8	122	156	74	105	1468
D 70	Rest	69	5.6	81	119	74	93	260
	300	108	10.9	101	136	71	96	944
	600	150	14.9	99	165	83	112	1635
D 74	Rest	63	5.7	90	149	86	111	292
	300	95	9.6	101	170	89	120	1007
	600	130	13.3	102	206	107	146	1744
D 77	Rest	92	8.1	88	133	71	97	—
	300	123	10.0	81	158	73	103	970
	600	150	13.3	89	182	82	113	1386
D 78	Rest	55	6.5	118	121	68	89	304
	300	86	9.8	114	139	74	99	959
	600	114	12.1	106	160	79	110	1422
D 79	Rest	63	6.6	105	126	74	94	337
	300	86	11.0	128	152	75	102	1096
	600	121	14.9	123	205	92	126	1799
D 80	Rest	54	6.5	120	116	64	84	174
	300	96	11.1	116	140	77	101	996
	600	140	16.7	119	194	93	120	1663
D 81	Rest	74	5.9	80	182	97	134	257
	300	98	8.0	[illegible]	209	107	149	625
	600	137	10.0	73	247	123	181	1473
D 83	Rest	83	6.5	78	125	78	102	301
	300	111	9.3	84	160	86	115	763
	600	155	13.6	88	204	99	137	1191
D 85	Rest	84	5.7	68	127	76	96	308
	300	135	10.4	77	161	92	116	787
	600	—	—	—	—	—	—	—

Table VI (continued)

Case No		Arterial O_2 sat (%)	Arterial CO tension (mm Hg)	pH	Stand bicarb (mE/l)	Haemo-globin conc. (g/100 ml)	Haema-tocrit value (%)	Venti-lation (l/min)	RQ	Blood sugar (mg/100 ml)
D 56	Rest	98.1	40.5	7.425	25.5	12.8	43	9.7	0.79	185
	300	97.7	44.5	7.360	23.0	15.3	45	23.4	0.94	168
	600	98.4	41.0	7.310	19.5	15.9	46	45.6	1.00	150
D 59	Rest	98.6	34.0	7.430	24.0	13.9	40	7.8	0.77	298
	300	96.2	36.0	7.420	24.0	14.3	41	22.6	0.81	294
	600	96.3	34.5	7.380	21.0	14.8	42	41.1	0.97	297
D 61	Rest	98.5	34.0	7.460	25.0	17.4	47	10.7	0.97	*239
	300	92.4	50.0	7.325	23.0	17.5	48	17.9	0.82	*210
	600	98.2	42.0	7.290	19.0	16.8	50	43.3	1.07	*194
D 66	Rest	93.8	28.5	7.540	28.5	15.6	47	10.4	0.86	40
	300	95.0	38.5	7.403	23.5	16.4	50	35.1	0.88	39
	600	98.6	39.0	7.385	23.5	16.4	50	35.1	0.88	39
D 68	Rest	98.4	43.0	7.390	24.5	15.3	45	9.0	0.80	154
	300	96.6	42.5	7.375	23.5	15.7	46	20.0	0.83	155
	600	96.9	41.0	7.370	22.5	15.6	46	36.6	0.92	134
D 70	Rest	95.1	44.5	7.385	24.5	13.1	43	6.9	0.84	74
	300	93.0	45.0	7.365	23.5	13.4	44	22.7	0.92	71
	600	92.6	42.5	7.350	22.0	13.5	45	37.8	0.91	77
D 74	Rest	98.5	34.0	7.410	22.0	14.6	44	8.2	0.79	110
	300	97.6	45.0	7.350	22.5	14.6	44	20.4	0.80	90
	600	98.5	38.0	7.340	20.0	14.9	46	41.6	0.97	80
D 77	Rest	95.7	42.0	7.380	23.5	13.0	46	—	—	222
	300	98.3	41.5	7.360	22.5	13.9	41	21.6	0.82	211
	600	99.8	42.0	7.345	21.5	13.2	40	35.6	0.93	204
D 78	Rest	96.3	36.0	7.415	23.0	14.7	45	7.3	0.75	139
	300	97.6	32.0	7.430	22.0	14.5	45	20.0	0.82	122
	600	97.0	31.5	7.400	19.0	15.3	47	34.7	0.93	96
D 79	Rest	—	—	—	—	14.9	44	9.6	0.74	180
	300	—	—	—	—	14.9	45	25.1	0.80	172
	600	—	—	—	—	14.9	47	43.5	0.87	160
D 80	Rest	91.2	44.0	7.388	24.5	14.8	43	7.3	0.73	238
	300	97.1	48.5	7.355	24.0	15.3	44	20.3	0.91	222
	600	92.8	46.5	7.325	22.0	15.5	47	32.2	0.94	188
D 81	Rest	96.4	37.0	7.360	20.0	15.7	46	6.0	0.74	245
	300	96.0	34.0	7.330	18.5	15.6	47	15.7	0.87	234
	600	97.7	37.0	7.300	18.0	15.8	50	42.8	1.00	220
D 83	Rest	96.3	40.5	7.370	22.0	15.6	46	7.6	0.71	304
	300	89.2	40.0	7.340	21.0	16.0	47	19.1	0.85	279
	600	89.0	33.0	7.280	16.5	16.4	51	35.6	0.93	275
D 85	Rest	99.6	35.5	7.435	24.5	15.0	45	8.1	0.87	294
	300	99.0	32.0	7.420	22.5	14.7	46	19.2	0.93	264
	600	—	—	—	—	—	—	—	—	—

Table VI (continued)

Case No		Arterial O sat (%)	Arterial CO tension (mm Hg)	pH	Stand bicarb (mE/l)	Haemoglobin conc (g/100 ml)	Haematocrit value (%)	Ventilation (l/min)	RQ	Blood sugar (mg/100 ml)
D 23	Rest	94 4	40 0	7 380	23 0	14 5	—	6 9	0 85	*200
	300	95 5	40 0	7 350	21 0	14 8	—	—	—	*190
	600	97 8	39 0	7 350	21 0	15 8	—	32 3	0 88	*180
D 24	Rest	99 1	43 0	7 410	24 5	13 8	42	6 9	0 77	*240
	300	98 4	41 0	7 390	23 0	14 0	43	21 7	0 80	*230
	600	97 7	44 0	7 350	21 0	14 9	45	36 1	0 86	*190
D 26	Rest	95 5	38 5	7 370	22 0	14 0	44	8 4	0 74	224
	300	92 6	38 5	7 370	22 0	14 4	45	19 8	0 77	229
	600	94 5	39 0	7 360	22 0	14 6	47	—	—	221
D 27	Rest	100 0	37 0	7 420	23 0	13 8	40	9 4	0 76	178
	300	98 6	35 0	7 425	23 0	14 2	41	23 3	0 80	181
	700	98 8	30 0	7 430	21 0	15 1	41	53 1	0 98	164
D 29	Rest	98 7	43 0	7 400	25 0	13 6	42	7 5	0 81	* 83
	300	99 3	43 0	7 382	24 0	14 5	43	18 7	0 74	* 73
	600	99 1	40 0	7 360	22 0	14 8	44	30 1	0 94	* 69
D 30	Rest	95 7	38 5	7 445	26 0	13 9	40	7 0	0 79	*123
	300	94 2	44 0	7 385	24 0	14 5	43	16 2	0 78	* 79
	600	94 8	48 0	7 345	23 0	14 8	44	38 2	0 89	* 65
D 31	Rest	98 0	42 0	7 380	23 5	15 1	43	6 2	0 76	—
	300	91 1	41 0	7 360	22 0	15 9	44	23 1	0 87	—
	600	—	—	—	—	—	—	—	—	—
D 32	Rest	100 0	40 0	7 410	24 5	14 2	40	7 2	0 80	*107
	300	95 6	41 0	7 390	25 0	14 9	42	—	—	*106
	600	95 8	40 0	7 380	23 0	15 2	43	—	—	* 90
D 40	Rest	94 5	40 5	7 405	24 5	14 2	44	8 7	0 81	*182
	300	94 7	38 0	7 379	24 0	15 1	46	25 2	0 96	*156
	600	99 4	38 0	7 355	21 0	15 1	47	46 1	1 12	132
D 44	Rest	98 5	30 5	7 480	24 5	15 1	42	10 3	0 99	117
	300	97 9	37 0	7 420	24 0	15 3	43	16 5	0 83	109
	600	94 6	38 0	7 390	22 5	15 4	44	40 0	0 90	89
D 46	Rest	92 9	40 5	7 445	27 0	14 2	44	8 1	0 79	—
	300	92 5	39 0	7 415	24 0	15 5	43	20 0	0 86	—
	600	90 8	38 0	7 420	24 0	15 9	45	34 8	0 96	—
D 50	Rest	96 6	40 5	7 390	24 0	12 5	38	6 5	0 84	*133
	300	92 7	43 0	7 360	23 0	12 7	40	24 3	0 93	*108
	600	—	—	—	—	—	—	—	—	—
D 52	Rest	96 3	42 0	7 385	24 0	13 0	40	5 9	0 77	114
	300	98 8	45 0	7 370	24 0	13 3	40	17 4	0 81	73
	600	95 1	43 5	7 350	22 5	13 1	42	33 6	0 97	61
D 54	Rest	100 4	37 0	7 400	23 0	14 4	42	7 5	0 78	194
	300	98 0	37 5	7 375	22 5	14 5	44	17 3	0 78	179
	600	90 4	40 0	7 360	22 0	14 7	44	31 1	0 79	168

Table VI (continued)

Case No		Arterial O sat (%)	Arterial CO tension (mm Hg)	pH	Stand bicarb (mE/l)	Haemoglobin conc (g/100 ml)	Haematocrit value (%)	Ventilation (l/min)	RQ	Blood sugar (mg/100 ml)
D 56	Rest	98.1	40.5	7.425	25.5	12.8	43	9.7	0.79	185
	300	97.7	44.5	7.360	23.0	15.3	45	23.4	0.94	168
	600	98.4	41.0	7.310	19.5	15.9	46	45.6	1.00	150
D 59	Rest	98.6	34.0	7.430	24.0	13.9	40	7.8	0.77	298
	300	96.2	36.0	7.420	24.0	14.3	41	22.6	0.81	294
	600	96.3	34.5	7.380	21.0	14.8	42	41.1	0.97	287
D 61	Rest	98.5	34.0	7.460	25.0	17.4	47	10.7	0.97	*239
	300	92.4	50.0	7.325	23.0	17.5	48	17.9	0.82	*210
	600	98.2	42.0	7.290	19.0	16.8	50	43.3	1.07	*194
D 66	Rest	93.8	28.5	7.540	28.5	15.6	47	10.4	0.86	40
	300	95.0	38.5	7.403	23.5	16.4	50	35.1	0.88	39
	600	98.6	39.0	7.385	23.5	16.4	50	35.1	0.88	39
D 68	Rest	98.4	43.0	7.390	24.5	15.3	45	9.0	0.80	154
	300	96.6	42.5	7.375	23.5	15.7	46	20.0	0.83	155
	600	96.9	41.0	7.370	22.5	15.6	46	36.6	0.92	134
D 70	Rest	95.1	44.5	7.385	24.5	13.1	43	6.9	0.84	74
	300	93.0	45.0	7.365	23.5	13.4	44	22.7	0.92	71
	600	92.6	42.5	7.350	22.0	13.5	45	37.8	0.91	77
D 74	Rest	99.5	34.0	7.410	22.0	14.6	44	8.2	0.79	110
	300	97.6	45.0	7.350	22.5	14.6	44	20.4	0.80	90
	600	98.5	38.0	7.340	20.0	14.9	46	41.6	0.97	[illegible]
D 77	Rest	95.7	42.0	7.380	23.5	13.0	46	—	—	222
	300	98.3	41.5	7.360	22.5	13.9	41	21.6	0.82	211
	600	99.8	42.0	7.345	21.5	13.2	40	35.6	0.93	204
D 78	Rest	96.3	36.0	7.415	23.0	14.7	45	7.3	0.75	139
	300	97.6	32.0	7.430	22.0	14.5	45	20.0	0.82	122
	600	97.0	31.5	7.400	19.0	15.3	47	34.7	0.93	96
D 79	Rest	—	—	—	—	14.9	44	9.6	0.74	180
	300	—	—	—	—	14.9	45	25.1	0.80	172
	600	—	—	—	—	14.9	47	43.5	0.87	160
D 80	Rest	91.2	44.0	7.388	24.5	14.8	43	7.3	0.73	238
	300	97.1	48.5	7.355	24.0	15.3	44	20.3	0.91	222
	600	92.8	46.5	7.325	22.0	15.5	47	32.2	0.94	188
D 81	Rest	96.4	37.0	7.360	20.0	15.7	46	6.0	0.74	245
	300	96.0	34.0	7.330	18.5	15.6	47	15.7	0.87	234
	600	97.7	37.0	7.300	18.0	15.8	50	42.8	1.00	220
D 83	Rest	96.3	40.5	7.370	22.0	15.6	46	7.6	0.71	304
	300	89.2	40.0	7.340	21.0	16.0	47	19.1	0.85	279
	600	89.0	33.0	7.280	16.5	16.4	51	35.6	0.90	275
D 85	Rest	99.6	35.5	7.435	24.5	15.0	45	8.1	0.87	294
	300	99.0	32.0	7.420	22.5	14.7	46	19.2	0.93	264
	600	—	—	—	—	—	—	—	—	—

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From the Department of Clinical Physiology, Lasarettet, Lund, Sweden

On the Accuracy of Indirect Auscultatory Blood Pressure Measurements during Exercise

by

T KARLEFORS R NILSÉN AND H WESTLING

In recent years the functional analysis of diseases of the cardiovascular system is often extended to conditions prevailing during physical exercise This analysis can be made in detail and include e g measurements of cardiac output and pressures in the systemic and the pulmonary circulation However, for several purposes a relatively simple analysis of the patient s reaction to exercise is satisfactory Such tests are usually performed on a tread-mill or a bicycle ergometer and generally include measurements of the heart rate and the respiratory frequency, recording of the electrocardiogram and sometimes studies of the gas exchange Such tests performed on a bicycle ergometer are now fairly common in Scandinavia Measurements of the arterial blood pressure are not made routinely during these tests possibly because of the difficulties in measurement

For various reasons it appeared to be desirable, e g in studies of arterial hypertension (e g 6, 10) to obtain some idea about the blood pressure reaction to a standardized exercise test There are observations which indicate that it is possible to measure brachial arterial pressures by the indirect method during graded exercise on a bicycle ergometer (3, 8, for references and discussion, see 5) The values obtained are of a reasonable magnitude when compared with subsequent direct measurements in connection with heart catheterization (12) On the other hand Henschel, de la Vega and Taylor (4) found considerable differences between indirectly and directly measured arterial pressures during and after exercise

Therefore, it was thought necessary to compare in more detail the arterial pressure measured by the auscultatory method with that measured directly by an indwelling arterial catheter The results of such simultaneous measurements in a mixed group of hospital patients are presented here Results in patients with valvular and congenital heart disease and in diabetes mellitus (7) will be reported separately

METHODS

All subjects were examined at rest, lying on a couch, and during exercise in the sitting

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METHODS

All subjects were examined at rest lying on a couch and during exercise in the sitting

position on an electrically braked ergometer (5) The test was carried out essentially as described by Sjostrand, 1960, (11)

Indirect measurement of the arterial pressure was usually performed in the right arm with a blood pressure cuff measuring 12×49 cm (rubber balloon 10,5×30 cm) and a mercury manometer During measurements in the recumbent position the patient's arm was kept approximately at mid thoracic level This means that the middle part of the blood pressure cuff was approximately 5 cm below the sternal angle The systolic pressure was noted at the point where Korotkow sounds appeared regularly Diastolic pressure was noted at the point where the Korotkow sounds disappeared entirely Measurements with Korotkow sounds present down to very low levels or to zero pressure were not used since it was found difficult to state clearly where the sounds changed character especially during exercise During exercise the patient was instructed to keep the arm relaxed with the elbow supported by the examiner's hand The level of the blood pressure cuff during exercise was approximately at the level of the sternal insertion of the fourth rib Measurements of blood pressure during exercise were performed every second minute The values given are as a rule those taken at the fourth minute of exercise

A polythene tube (PE 160, 44 cm long) was inserted into one brachial artery usually the left, using the percutaneous technique described by Berneus et al 1954 (2) The left arm was used whenever possible, to diminish the discomfort after the arterial puncture Pressures were registered using a variable inductance manometer (Elema Stockholm Sweden) The zero reference level was taken at 5 cm below the sternal angle in the recumbent position During exercise the reference level was placed approximately at the sternal insertion of the fourth rib at about the level of the middle part of the blood pressure cuff on the other arm Mean pressures were obtained by electrical integration

A correlation between indirect and direct measurement was obtained by the use of a test signal which was activated by an assistant both at the appearance of Korotkow sounds and at their disappearance This close time correlation was particularly necessary in patients with large respiratory variations in arterial pressure The values for indirect arterial blood pressure were noted and the directly measured pressure were calculated independently by another assistant

MATERIAL

The present material consists of 38 cases Seven of these were healthy subjects who volunteered for the investigation The rest were hospital patients, who for some reason or another underwent examination involving arterial puncture mostly because of hypertension (15 patients) or pulmonary disease (8 patients)

RESULTS[1])

1 Measurements at rest

At rest there was a good agreement between the auscultatory and the directly recorded systolic pressure The auscultatory value was on the average 1 7 mm Hg higher, the difference was not significant (Table I) For the diastolic pressures a significant systematic difference was obtained, with the directly recorded pressures on the average 11 3 mm Hg lower than the indi

Table I

Pressures at rest 38 cases
Average values ± S E M mm Hg

	Directly measured pressure	Difference auscult — directly measured
Systolic	148 ± 5 3	1 7 ± 1 4
Diastolic	85 ± 3 3	11 3 ± 1 6

[1]) Primary observations and other details may be requested from the authors

rectly measured pressures This occurred in spite of the fact that the auscultatory pressure was taken at the point of disappearance of Korotkow sounds The inaccuracy of the indirectly estimated diastolic pressure was therefore larger, especially when calculated as percentage, than that of the systolic pressure The dispersion of the indirectly measured diastolic pressures around their mean was also larger than the dispersion of the systolic pressures

The arm circumference of the subject had no detectable influence on the accuracy of the estimation of systolic pressure by the indirect method On the other hand for the diastolic pressure the mean overestimation by the indirect method was 15 mm Hg in 9 subjects with thick arms (> 30 cm in circumference) whereas the mean overestimation in 9 subjects with lean arms (< 26 cm in circumference) was only 7 5 mm Hg In the intermediate group (arm circumference 26 5—29 5 cm) the corresponding figure was 10 mm Hg

The correlations between the intra arterially measured mean pressure and the systolic and diastolic pressures measured directly and indirectly were also studied It was apparent that the directly measured diastolic pressure showed the best correlation to the intra arterial mean pressure whereas the two indirectly recorded pressures were less well correlated to the mean pressure Nevertheless the auscultatory systolic pressure had a fair degree of correlation to the intra arterial mean pressure (correlation coefficient [illegible]89)

2 Measurements during exercise

There was no systematic trend for a difference in systolic pressure to occur during exercise All observations made are shown in Fig 1 The correlation

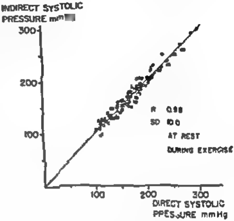

Fig 1 Comparison of indirect (auscultatory) and direct (intra arterial) systolic blood pressure at rest (crosses) and during exercise (circles) The regression line y = 0 99 X + 1 95 is drawn

between auscultatory and directly measured systolic pressures for the whole series of observations at rest and during exercise was 0 98 (125 observations) In the 17 subjects in which measurements were made during light, moderate and heavy exercise the average deviations amounted to a few mm of mercury with no systematic trend (Table II) It is thus apparent from the observations in this material that one can obtain a fair estimate of the brachial arterial systolic pressure during exercise by the indirect method

The diastolic pressures during exercise were often unmeasurable, i e the Korotkow sounds were present down

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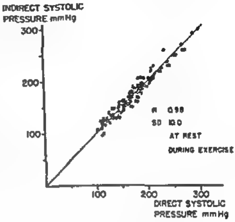

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Table II

Difference between auscultatory and directly measured systolic pressures in connexion with exercise

Light, moderate and heavy exercise refer to 300, 600 and 900 kpm/min for men and 200 400 and 600 kpm/min for women, respectively Mean values ± S E M are given in mm Hg

1 17 cases

	At rest	Light exercise	Moderate exercise	Heavy exercise
Difference auscultatory — directly measured systolic pressure	+3 1±2 3	—1 9±2 8	±0 0±2 3	+3 6±2 4
Average systolic pressure	139	162	181	191

2 21 cases

	At rest	Light exercise	Moderate exercise	4 min after exercise recumbent
Difference auscultatory — directly measured systolic pressure	+1 5±1 9	—3 4±2 8	+0 1±2 0	+6 2±1 8
Average systolic pressure	152	182	202	163

to zero pressure It therefore proved extremely difficult in some cases to obtain a clear definition of the diastolic pressure These values were therefore not used for analysis In those cases in which it was possible to demarcate "diastolic pressure" during exercise the values were often too low (deviations 10—20 mm) in comparison with the directly recorded diastolic pressures

Measurements after exercise were made only in a small number of patients In 21 cases were measurements available at four minutes after the cessation of exercise (Table II) Here a systematic difference between the two "systolic pressures" was noted, the indirect one being on the average 6 2 mm higher than the directly measured one In this group there was no systematic difference between the systolic pressures, measured by the two methods, before exercise and during light and moderate exercise

Fig 2 shows the relationship at rest and during exercise between the systolic pressure, measured indirectly, and the mean pressure, measured directly in the artery A relatively good corre-

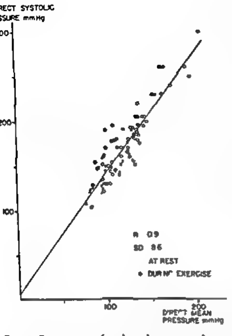

Fig 2 Regression of indirectly measured systolic blood pressure on the intra arterially measured mean pressure at rest (crosses) and during exercise (circles) The regression line y 1 36 X + 6 12 is drawn

lation between these two measurements is demonstrated with a correlation coefficient of 0 91 (125 observations)

DISCUSSION

An unexpected finding was the systematic difference at rest in the present material between the indirectly recorded diastolic pressures and the direct measurements Previous workers have generally found a good agreement between the pressure where Korotkow sounds disappear entirely and the correct diastolic pressure Results similar to those presented here were however obtained by Ragan and Bordley (9) and Berliner et al (2) An acceptable explanation for the errors in estimating the diastolic pressure cannot be given It is possible that the cuff measures in relation to the configuration of the arm are of importance since the error in the present series was larger in subjects with thick arms On the other hand systolic pressures were not affected In some subjects we have used a larger cuff (13 5 cm total width expansible rubber ballon 12 cm), but obtained similar results

We wish to stress the point that in our experiments the errors in indirect measurement of the diastolic pressure are relatively larger than those for the systolic pressure The errors may be so large as to influence the clinical handling of patients if too much emphasis is placed on the diastolic pressure The present observations strengthen the belief that it is advisable to measure the arterial blood pressure directly in selected cases of hypertension

Some minutes after cessation of the exercise test the systolic pressures measured by the indirect method were systematically larger than the directly measured pressures This discrepancy has been noted previously by Henschel et al (4) The difference 4 minutes after exercise was not unduly large but it may serve as warning that the complexity of the pressure variations in the arterial system is such that caution is always needed before accepting an indirect pressure measurement as a true value

We cannot forward any explanation why under the present conditions indirectly and directly measured systolic

pressures agree, whereas Henschel et al (4) found the indirect systolic pressure to be too *low* during exercise and much too *high* during the first minutes after it The fact that Henschel et al measured directly in the radial and indirectly in the brachial artery may, in addition to other methodological differences, be reasons for the divergent results

Our experience of the reasonably good agreement between indirect and direct systolic pressures during exercise do not hold for certain cases of heart disease, e g of the aortic valve A closer analysis of the influence of the form of the pulse wave and of other factors will be published separately

With the reservations mentioned above, we think that the present observations allow us to conclude that the systolic blood pressure can be measured indirectly during an ordinary exercise test with an error, which is not appreciably larger than that in measurements at rest Measurement of the systolic blood pressure increases the diagnostic information given by the exercise test The values for systolic blood pressure give some idea about the mean pressure to which the arterial tree is exposed during bodily exercise Therefore, indirect measurements of the systolic blood pressure during exercise have been used in this laboratory for screening purposes, e g in patients with diabetes mellitus (7) Patients in which suspicious findings are made during the ordinary exercise test should sometimes be subjected to a more detailed investigation using direct recording techniques

SUMMARY

The pressure in one brachial artery was measured directly through a polythene tube in the artery and indirectly by the auscultatory method in the other arm A good agreement was obtained between the systolic pressure, measured by these two methods, both at rest and during exercise Four minutes after exercise the indirect systolic pressure was significantly higher than the intra-arterially measured value The systolic pressure at rest and during exercise shows a fairly good correlation to the intra-arterially measured mean pressure

Reliable measurements of the diastolic pressure during exercise can often not be obtained by the indirect method

It is suggested that ordinary exercise tests for screening purposes in patients with suspected or manifest cardio-vascular disease should include measurement of the systolic blood pressure by the indirect method

ACKNOWLEDGEMENTS

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pressures agree, whereas Henschel et al (4) found the indirect systolic pressure to be too *low* during exercise and much too *high* during the first minutes after it. The fact that Henschel et al measured directly in the radial and indirectly in the brachial artery may, *in addition* to other methodological differences, be *reasons for the divergent results*.

Our experience of the reasonably good agreement between indirect and direct systolic pressures during exercise do not hold for certain cases of heart disease, e g of the aortic valve. A closer analysis of the influence of the form of the pulse wave and of other factors will be published separately.

With the reservations mentioned above, we think that the present observations allow us to conclude that the systolic blood pressure can be measured indirectly during an ordinary exercise test with an error, which is *not* appreciably larger than that in measurements at rest. Measurement of the systolic blood pressure increases the diagnostic information given by the exercise test. The values for systolic blood pressure give some idea about the mean pressure to which the arterial tree is exposed during bodily exercise. Therefore, indirect measurements of the systolic blood pressure during exercise have been used in this laboratory for screening purposes, e g in patients with diabetes mellitus (7). Patients in which suspicious findings are made during the ordinary exercise test should sometimes be subjected to a more detailed investigation using direct recording techniques.

SUMMARY

The pressure in one brachial artery was measured directly through a polythene tube in the artery and indirectly by the auscultatory method in the other arm. A good agreement was obtained between the systolic pressure, measured by these two methods, both at rest and during exercise. Four minutes after exercise the indirect systolic pressure was significantly higher than the intra-arterially measured value. The systolic pressure at rest and during exercise shows a fairly good correlation to the intra-arterially measured mean pressure.

Reliable measurements of the diastolic pressure during exercise can often not be obtained by the indirect method.

It is suggested that ordinary exercise tests for screening purposes in patients with suspected or manifest cardio-vascular disease should include measurement of the systolic blood pressure by the indirect method.

ACKNOWLEDGEMENTS

The assistance of Nurses E. Höglund and A. Månsson is gratefully acknowledged. The present work was supported by grants from the Swedish National Association against Heart and Lung diseases.

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Contents

Introduction

Hemiplegia due to cerebrovascular lesions often results in premature death or permanent disability. Some patients, however, recover and can resume their work.

The incidence of cerebrovascular diseases increases with age. In view of the increasing average duration of life and change in the shape of the population pyramid, the number of old persons will increase markedly (Åldringsvårdens läge, S O U 47 1963). This in turn implies the need of increased facilities for the care of patients with hemiplegia. Our resources are at present not sufficient. We need not only more hospital beds but also a more active attitude towards rehabilitation and measures to enable the patients to become less dependent or independent of personal help or to undergo vocational training. A rehabilitation programme should include, besides medical care, instruction and training of the patient, attention to environmental factors capable of improving the patient's performance.

The purposes of the present investigation were *firstly* to devise a method for analysing and assessing the disability of chronic hemiplegics, the degree of dependence of the disability on the environments in order to find out which patients are accessible to rehabilitation and what measures should be taken, and *secondly* to try the method to a series of patients with chronic hemiplegia.

Method

Brief survey of previous methods

Conventional descriptions of hemiplegia are usually dominated by medical data of diagnostic interest. But such data teach little of what the patient can or cannot do. Increasing possibilities of rehabilitation of hemiplegics have created a need of standardisable measuring methods to assess the disability of such patients from a functional point of view.

Moskowitz & McCann (1957) elaborated the Canadian Army's method which was afterwards taken up by the American Army. The original profile which gives a readily surveyable description of functional disability as based on certain medical characteristics was modified so as to be adaptable to elderly patients and patients with chronic diseases.

A more detailed method for judging functional disability from medical data was presented by Kaplan et al. (1960). In "A Guide to Evaluation of Permanent Impairment of Extremities and Back" (1958) the method is based entirely on medical impairment.

Data on a patient's medical status were supplemented by information on the patient's ability to manage his daily life, e.g. eating, dressing, personal hygiene and walking (Dinken 1947, Bennet 1949, Rinzler et al. 1951, Lawton 1956, the staff of Benjamin Rose Hospital 1959, Carroll 1962, Dinnerstein et al. 1965, Schoening et al. 1965).

Though these methods are comprehensive, they do not include such important items as type of family, conveniences and facilities available in the patient's home, economic situation, etc., all of which are necessary in the assessment of the sort of life the patient leads at home. McCoy & Rusk (1953) extended their method to include certain psychological, social and economic factors which were included in the evaluation of a rehabilitation rating, a single judgement on the overall social and physical adjustment of the individual. The authors stressed, however, that "this study did not attempt to evaluate the factors (psychiatric and social) as coefficients in the patient's situation except as overt action suggested their influence." The medical status was, however, limited to a report of the medical diagnosis.

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Lee et al. (1958), on the other hand, used a number of medical data and the patient's attitude to treatment, which they compared with the final disposition of the patient expressed in

the form of information on his performance such as "home active", "home medical care" and the like. The ability of the patient to look after himself and to walk is described. The importance of certain social factors is stressed, but they were not made the subject of a detailed analysis. No descriptions are given of the patients' homes.

Sokolow et al. (1958) described a detailed method including firstly, medical status, secondly, the activities of daily life, thirdly, certain psychological, social, vocational and economic factors, and, fourthly, certain other factors for evaluation of the "rehabilitation potential". The method does not include information about conveniences in the patient's home. The authors used a form made to fit into an IBM card with 80 columns and 12 items in each. They briefly outlined how the various data can be used but they gave no detailed account of the way in which they judged the accessibility of a given patient to rehabilitation. This method was revised and supplemented in 1959 (Sokolow et al.) and elaborated further in 1962 (Sokolow et al.). In their last paper these authors again stressed the importance of the social factors in the evaluation of disability, which, however, received little space in their schema.

Reed & Harvey (1964) used a method consisting of a detailed medical examination with determination of physical performance, psychological and certain social factors. But their method does not describe the patients' activities of daily life or the patients' homes.

Litman (1964) used not only medical status and motivation but also a larger number of psychological factors to analyse the cause of the variation in the results of rehabilitation. He gave no account of the patients' homes.

A method described by Andersen (1964) measures the physical handicap by the degree of loss of working capacity and the ratio between the number of handicapped capable of doing only a certain type of work and the possibilities of obtaining such work. Social adjustment was measured by the earned income, by an index for adjustment to the patients' occupation and by an index for household work. In a coordinate system with the social adjustment along the y axis and the degree of disability along the x axis, a certain degree of disability corresponded to an expected social adjustment (earned income). Deviation from the expected social adjustment is called degree of compensation and can be influenced by a number of psychological and social factors. The data included a detailed account of the patients' homes. The medical status is only briefly outlined and apart from information as to whether the patient uses a wheelchair nothing is said about the activities of daily living. Since the size of the earned income or index for housework is a measure of social adjustment the method is intended mainly for patients who are able to work or will sooner or later be able to do so.

Scales for different variables

Hereinafter medical status, activities of daily living, working capacity, psy-

chological and social factors are also referred to as variables

Several methods have been used for expressing impairment of such variables

Vague verbal descriptions of the variables in such methods are now being replaced more and more by precise definitions which are also expressed as numerical values placing the patients at definite levels on a rating scale The variables are described by ordinal scales which means that the scale is usually divided into 2—5 steps and though numbers are used for convenience they do not denote the size of the interval (Dinken 1947 Moskowitz & McCann 1957 Sokolow et al 1962 Dinnerstein et al 1965 Schoening et al 1965)

Some authors add the number of points for various subvariables of a certain activity and compare the value obtained with the maximum possible sum that can be achieved and calculate a percentage as a measure of disability (Dinken 1947 Binzler et al 1951) The staff of Benjamin Rose Hospital (1959) constructed an index which expresses the patient s relative dependence on personal help according to combinations of 6 different types of activities of daily living These combinations however include also medical data Carroll (1962) gives points for the different activities on the basis of relatively different ordinal scales and adds all the activities to form an over all score as an expression of the patient s ability to manage activities of daily life This overall score however includes some medical data Dinnerstein et al (1965) used a point scale graded according to the need of personal help for the various activities of daily living and adds the points to form a total sum In a method consisting of 5 main factors and devised in 1962 Sokolow et al use a special point system according to which 50 % for *e g* the medical factor means roughly the same functional disability as 50 % of the factor environment adjustment which consists of activities of daily living social situation and vocational situation Multiplication of the number of points for all the main 5 factors gives a percentage expressing total function The method was being tried out in 1962 when it was described as tentative

Comments Modern methods are becoming more and more multifacetted with more precise definitions of an increased number of descriptive variables such as medical data activities of daily living psychological and social factors all in an attempt to allow a better evaluation of functional disability The use of points for various factors and of ordinal scales is being used more and more The large variety of data has made it more difficult to assess the degree of disability of a patient at a glance This has led to attempts to devise methods allowing a ready impression of the patient s situation as a whole But then again it is difficult to form a clear conception of a patient simply from a single total sum It is questionable whether it is justified to add or multiply different

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patient X_1 are supposed to be adequate The patient has, among other things, to ascend a few steps to enter his home The level of the psychosocial factors is represented by point b_1 on the axis B and causes no change in the level of the point c_1 in either direction Thus for patient X_1 there is correspondence between the levels of the three main variables A B and C *i e* the levels are concordant

Patient X_2 has the same medical handicap as patient X_1 However his sociomedical performance c_2 is lower on the axis C *i e* it is less than expected from his medical status This deviation is presumably due to psychosocial factors which place him at a lower level b on the axis B The factors capable of lowering his sociomedical performance should thus be analysed so that they may be detected and if possible corrected

Patient X_3 who has the same medical handicap as patient X_1 and X_2 has a sociomedical performance which places him at a higher level c_3 and which is better than expected and thus he deviates positively probably because the psychosocial factors place him higher up the vertical at level b_3

In all 3 patients the medical status should be investigated in order to find out whether it is possible to improve the patient s position regarding level a_3

Every main variable is built up of certain subvariables influencing or capable of influencing the patient s functional disability Every subvariable thus represents for example the function of a limb ability to walk up steps or a deficiency of the patient s home Certain subvariables are graded *according to an ordinal scale* and the patient s position on the scale is estimated Instead of describing the levels verbally when possible the patient s position for a given variable will be *indicated by a number of points* the poorer the medical function socio medical performance or psychosocial factors the higher the number of points The point scale has five steps namely *0 1 10 100 and 1000* There is no direct mathematical relationship between the various grades of the scale Thus the figure 1000 does not mean a level at which the patient is 10 times worse than one at a level of 100 but simply marks an interval between the two levels

As mentioned the point scale has five steps but *for each subvariable* it is confined to four levels The score 0 always means absence of medical handicap, of decrease in the performance or of psychosocial deficiency Otherwise the scale can rise slowly or rapidly and terminate at lower or higher point levels according to the disabling effect indicated by the character of the subvariable Such subvariables of medical status as can dominate the patient s functional disability are given a higher number of points than those subvariables that are of subordinate importance *For example* a severe organic brain syndrome is judged as a *greater medical handicap* than a *paralysed arm* and will place the patient at the 1000 point level while the paralysis will place him at the 100 point level *If* a patient is

See page 15

variables whether they are related or not

In a method consisting of a very large number of variables some of them may be missed and the significance of such errors may be difficult to evaluate since such variables differ in importance. This makes the search for variables relevant to the patient's functional disability difficult and thereby also attempts at causal rehabilitation.

A method covering certain well defined variables which can be taken together according to their character to form well defined main variables allowing systematic comparisons of the variables would improve the possibility of obtaining information necessary for assessing a patient's accessibility to rehabilitation.

Analytical model, main variables, subvariables and numerical measurements

It might be convenient first to define some of the terms used in this presentation. Medical status or function is to be understood as the medical neurological and psychiatrical condition of a hemiplegic. Sociomedical performance is a blanket term to define the patient's ability *e g* walking self care and vocational activity. Psychosocial factors is an expression used to describe *e g* the patient's motivation, *overprotective attitude of his relatives* the presence or absence of conveniences in his home or the patient's socio economic position etc.

With adequate rehabilitation some

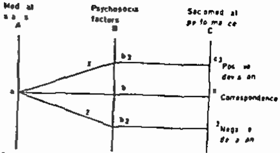

Fig 1 Model [illegible] ween the three main variables

hemiplegics can entirely or partly resume the life they led before the onset of hemiplegia. The goal of rehabilitation should be placed as high as the patient's medical status will allow. Proper evaluation of a patient's accessibility to rehabilitation, the choice of the goal of rehabilitation and the type and extent of treatment necessary require detailed information of the patient's medical status, *sociomedical performance and psychosocial factors*.

The model in Fig 1 shows schematically how a patient's disability and accessibility *to rehabilitation are estimated*. The axes, the main variables A, B and C represent *medical status*, psychosocial factors and sociomedical performance respectively. *The higher* the level of a patient along any of these axes the better his situation.

Let us first consider patient X, whose medical status places him at the level a on axis A meaning that he is somewhat handicapped *e g* function of the leg is moderately decreased. Supposing that this handicap causes a corresponding decrease of his sociomedical performance *e g* moderately decreased ability to walk upsteps and placing him at the level of c_1 on the axis C. The psychosocial factors for

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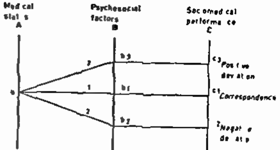

Fig. 1. Model illustrating interplay between the three main variables.

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Notes were also made of the side of the paresis and duration of the disease

1—2 Function of arm and leg

The function of the limbs was examined in accordance with Feldman et al (1962) The evaluation was based on the following factors muscle function spasticity contractures

Muscle function was classified as

normal or good the muscle or muscles were able to move the part through the full range of motion against maximal or nearly maximal manual resistance

fair the muscle or muscles were able to move the part through the full range of motion against gravity but could not do so against more than minimal manual resistance

below fair the muscle or muscles were unable to move the part against gravity or could do so through such a limited range of motion that they were virtually non functioning

Spasticity was classified as

slight present but not functionally significant

severe present and functionally significant

Contracture was considered as *disabling* when it significantly interfered with the function of the affected limb

The presence of disabling contractures requires that the function of the extremity be classified as pronouncedly decreased

The above components muscle function spasticity and contractures were evaluated according to a method described by Feldman et al (1962) and given in slightly modified form in Table 1

According to this method four levels are recognised and alotted a point value

Function of arm or leg	Points
Full	0
Slightly decreased	1
Moderately decreased	10
Pronouncedly decreased	100

Comments The highest level used was 100 points because even pronounced reduction of function of an extremity need not completely disable the patient (Lee et al 1958) and secondly it indicates treatment if the patient is otherwise accessible to rehabilitation If it is an upper limb whose function is *pronouncedly decreased* the patient can be trained to do most necessary things with the healthy limb (Rusk 1964 Levenson 1965) If it is a lower limb whose function is *pronouncedly decreased* it may be possible by adequate treatment to teach the patient how to walk or use a wheelchair In the event of severe *spasticity* or *severe contracture* in the knee joint with an extension defect the prospects of the patient recovering ability to walk are poor (Lee et al 1958 Hoerner 1958 Peszczynski 1963 Rusk 1964)

In the evaluation of the upper limb the state of the hand is important (Peszczynski & Bruell 1960) Even if the function of the upper and lower arm is satisfactory the function of the entire limb is pronouncedly decreased

placed at the 1000 level of the scale for medical status, it also means that the prospects of rehabilitation are poor

By systematic comparison between the subvariables belonging to the 3 main variables medical status, socio-medical performance and psychosocial factors the *patient s functional disability* can be described and analysed The patients are also analysed by systematic comparison between such subvariables as can be related to one another and which belong to the same main variable

The various steps of the scale also enable simultaneous description of several subvariables in a given case For example a severe organic brain syndrome places the patient at the 1000 point level and paralysis of one arm at the 100 point level Since the patient's ability to lead a more or less independent life is dependent upon these two subvariables, the functional disability of the patient could be described with the point constellation 1100 If the patient also has moderate paresis of one leg (10 points) the constellation will be 1110 If he also has hemianopsia (10 points) and slight dysphasia (1 point) his point constellation will be 1121 This patient is thus described by one subvariable at each of the levels 1000 100 and 1 point and two subvariables at a level of 10 Thus point constellation is not to be regarded as a total of various values but rather as a series of digits

Thus, if all the subvariables of variable A be taken together it will give a point constellation which is a rough measure of medical status of the patient According to the constellation the patient is assigned to one of the medical status groups I, II, III or IV This roughly indicates the position of the patient regarding the main variable medical status The contents of these groups are described on page 20

Certain subvariables of the variables sociomedical performance and psychosocial factors may likewise be taken together to form point constellations and classification of the patient The scope of these groups is described in further detail on pages 22 and 29

Other subvariables, for which point levels would serve no purpose are described verbally or graphically

Medical status

The variable medical status describes *the patient s medical, neurological, and* psychiatric situation It is made up of a number of subvariables All the subvariables selected represent considerable characteristics of hemiplegia Moreover, a special subvariable was used to describe co existing diseases or symptoms other than hemiplegia The examiner s opinion of a certain aspect of the patient s disability is given under each subvariable

The subvariables used were

1—2 Function of the arm respectively leg of the paretic side
3 Cerebral function
4—6 Communication (speech vision and hearing)
7—8 Bladder and bowel control
9 Co existing disease or symptoms not due to hemiplegia

if the hand is moderately or pronouncedly paretic (Carroll 1965).

Decreased dorsal flexion of the foot was considered less important if the limb was otherwise functionally satisfactory.

3. *Cerebral function*

Cerebral function was judged after an examination of the patient and an interview with his relatives or people looking after him. Evaluation was based on each of the following observations, each with 3 corresponding levels (key 1).

According to the result of the verbal description of each of the above observations and against the background of the importance of cerebral function for the patient's ability to cooperate actively in rehabilitation the patient's cerebral function was graded as follows:

Cerebral function	*Points*
Full	0
Decreased	10
Pronouncedly decreased	1000

Comments. Cerebral function was estimated on the basis of the literature and clinical experience.

Evaluation of the cerebral function of hemiplegics is important but difficult (Fisher 1961, Fink & Hallenbeck 1962, Ullman 1962). In such a field investigation the examination must be confined to a few observations and does not include complicated test methods which fatigue the patient. The primary function of the examination was to find out in which patients cerebral function was so decreased that the patients were not accessible to active rehabilitation. These patients were given 1000 points. Patients who were judged as having decreased cerebral function but not so decreased as to prevent rehabilitation, were assigned to an intermediate group (10 points). When accessibility to rehabilitation owing to decreased cerebral function was doubtful the patient was assigned to the 10 point group. To this group then were assigned all those with decreased cerebral function and in whom it was thought that they were accessible to psychiatrical treatment (Ullman 1962, Rusk 1964). The 100 point level was excluded because the use of more than 3 levels would imply a lower degree of reliability. The intermediate group given 10 points thus covers a wide range. Further differentiation of the patients in this group was considered to fall within the field of psychiatry.

Since most of the hemiplegics were of advanced age and since it is known that organic brain lesions were present, the criteria selected were dominated by such symptoms as are common among elderly patients with organic brain syndrome. These symptoms are largely those described by Klein & Mayer-Gross (1957), Allison (1962), Ullman (1962), Rusk (1964), Sjögren (1961). Some of the symptoms overlapped. They are intentionally selected so as to reflect the patient's accessibility to rehabilitation. For instance, if the patient's memory for recent events is so impaired that he

Table 1 Function of arm or leg as judged from muscle function spasticity and disabling contractures (Based on Feldman et al 1962)

Muscle function	Spasticity		
	None	Present but not functionally significant	Present and functionally significant
Normal/Good	Full function [a]	Slightly decreased function [a]	Moderately decreased function [a]
Fair	Moderately decreased function [a]	Moderately decreased function [a]	Pronouncedly decreased function
Below fair	Pronouncedly decreased function	Pronouncedly decreased function	Pronouncedly decreased function

[a] In addition to degree of muscle function and/or spasticity the presence of disabling contractures requires that the function of the extremity be classified as pronouncedly decreased

Key 1

	Full	Decreased	Pronouncedly decreased
a) Ability to give his history			
b) Memory for recent events			
c) Ability to cooperate			
d) Ability to learn			

	None	Slight to moderate	Pronounced
e) Emotional lability			
f) Increased fatiguability			
g) Other signs of organic brain syndrome			
h) Other functional disturbances such as psychoneurosis psychosis psychopathy defective intelligence etc			

Key 2

Dysphasia	Type and points Expressive	Impressive	Global	Definition
None	0	0	0	
Slight	1	1	—	Slight difficulties in understanding and/or making himself understood
Moderate	10	100	—	Moderate difficulties in understanding and/or making himself understood
Pronounced	100	100	100	Inability to understand and/or make himself understood

the treatment of the condition for rehabilitation in general, e.g. training of walking, self care, etc. Impressive dysphasia was therefore given 100 points even when it was only moderate. Owing to the nature of global dysphasia it could not be graded into different degrees of severity. The highest value for all types of dysphasia was the 100 point level.

Marks et al. (1957) when treating 333 patients with *different types of dysphasia* found improvement in 50 %. The best results were obtained in patients with expressive dysphasia. In a study of the relation between improvement of speech and physical activities (self care and ability to walk) Boone (1961) found a significant relation between poor improvement of speech and poor improvement of physical activities. One group of patients made *good improvement* regarding their speech and physical activities while another group despite poor improvement of physical activities made good *or excellent* progress regarding speech. Many patients became independent as far as self care and walking is concerned and continued to have global dysphasia.

There is thus reason to give patients with dysphasia an opportunity for rehabilitation provided that the goal of rehabilitation and the duration of treatment be adjusted according to the results of repeated examination and to effect of treatment.

b) Vision

The vision was examined by allowing the patient with his glasses, if he used any, to read aloud from the newspaper. He was *examined for visual* field defects according to the method of Donders. The results were recorded in the following way (Key 3).

Comments. Satisfactory vision is necessary for rehabilitation of elderly persons especially if they have difficulties in walking, decreased muscle *posture* sense or astereognosis. Hemianopsia usually retards rehabilitation but after a certain time the patient can usually

cannot remember what he learned the day before, the *prospects of rehabilitation are poor* (Knapp 1959, Adams & Hurwitz 1963)

Analysis of the cause of decreased *function and classification of the patients according to the diagnosis was not considered a primary necessity The further psychiatric investigation,* when indicated, should be performed by a psychiatrist (Ullman 1962, Rusk 1964)

The poor prognosis of mentally deteriorated cases has been stressed, among others, by Rankin (1957) Knapp (1959) and Rusk (1964) pointed out that brain damage limits the final goals of rehabilitation The poor results of rehabilitation of patients with extensive organic brain damage have also been emphasised by Fisher (1961), and Feldman et al (1962) In series where the patients have undergone rehabilitation, patients with severe brain damage have been excluded (Lee et al 1958, Ullman 1962 and Litman 1964) Adams & Hurwitz (1963) applied Allison s schema (1962) and described "mental barriers of those patients who could *not learn to look after themselves* or walk In a mixed neurological series with certain psychical symptoms Fallström (1964) compared the prognosis of rehabilitation of patients with and without cerebrally located disease He found that with cerebrally located disease there seems to be a generally reliable relation between psychic symptoms and unfavourable rehabilitation prognosis'

In view of the experiences gained from the above sources it was considered reasonable that the method provides a possibility to ascertain whether or not cerebral function is pronouncedly decreased Spontaneous fluctuations in a given patient, deterioration because of transfer of the patient to new surroundings and reduction of external stimuli implied by institutionalisation usually are sources of error which can result in erroneous evaluation of the patient's cerebral function In order to avoid such erroneous evaluation the relatives or the person looking after him were always interviewed It was also considered important to assign patients requiring psychiatric treatment to a special group

The procedure used in the evaluation of the cerebral function was only partly applicable regarding patients with dysphasia Such patients were also judged from the general impression they gave their appearance and their behaviour and from information from relatives or people looking after them

4—6 *Communication*

This subvariable comprised the speech *vision and hearing*

4) *Speech*

Decreased ability to speak is to be understood here as dysphasia Three types were recognised mainly expressive mainly impressive and *global The following degrees and definitions were* used (Key 2)

Comments Expressive dysphasia was not given *so many points* as the impressive type because ability to understand the spoken word is important in

Key 2

Dysphasia	Type and points			Definition
	Expressive	Impressive	Global	
None	0	0	0	
Slight	1	1	—	Slight difficulties in understanding and/or making himself understood
Moderate	10	100	—	Moderate difficulties in understanding and/or making himself understood
Pronounced	100	100	100	Inability to understand and/or make himself understood

the treatment of the condition for rehabilitation in general, *e.g.* training of walking, self care etc. Impressive dysphasia was therefore given 100 points even when it was only moderate. Owing to the nature of global dysphasia it could not be graded into different degrees of severity. The highest value for all types of dysphasia was the 100 point level.

Marks et al. (1957) when treating 333 patients with different types of dysphasia found improvement in 60 %. The best results were obtained in patients with expressive dysphasia. In a study of the relation between improvement of speech and physical activities (self care and ability to walk) Boone (1961) found a significant relation between poor improvement of speech and poor improvement of physical activities. One group of patients made good improvement regarding their speech and physical activities while another group despite poor improvement of physical activities made good or excellent progress regarding speech. Many patients became independent as far as self care and walking is concerned and continued to have global dysphasia.

There is thus reason to give patients with dysphasia an opportunity for rehabilitation provided that the goal of rehabilitation and the duration of treatment be adjusted according to the results of repeated examination and to effect of treatment.

a) Vision

The vision was examined by allowing the patient with his glasses, if he used any, to read aloud from the newspaper. He was examined for visual field defects according to the method of Donders. The results were recorded in the following way (key 3).

Comments. Satisfactory vision is necessary for rehabilitation of elderly persons especially if they have difficulties in walking, decreased muscle posture sense or astereognosis. Hemianopsia usually retards rehabilitation but after a certain time the patient can usually

Key 3

Vision	Points	Definition
Full	0	Patient could read without difficulty
Slightly decreased	1	Patient could read with some difficulty
Moderately decreased	10	Patient could read only headlines and/or had hemianopsia
Pronouncedly decreased	100	The patient could not read headlines

adjust himself and learn to take care of himself and to walk (Peszczynski 1963) A hemiplegic with impaired vision usually requires examination by an ophthalmologist in order to find out whether vision can be improved by adequate treatment In the light of these observations the scale for vision was limited to the 100 point level

6) *Hearing*

Hearing was judged in the following way (Key 4)

Comments Impairment of hearing is common in elderly patients It can act as a barrier between the patient and his entourage to a degree varying with the severity of impairment of hearing A patient with impaired hearing usually requires examination by a specialist If hearing can be improved, rehabilitation will be easier The scale was limited to the 100 point level

General comments on communication

Decreased ability to communicate must, as far as disability is concerned, be viewed from two angles Firstly, it is disabling because it limits the patient's possibility to keep in touch with his entourage and may result in isolation of the individual Secondly it makes rehabilitation more difficult since the latter requires active participation of the patient Rehabilitation is largely a learning process and communication between the patient and the instructor is necessary

It is therefore necessary to evaluate

Key 4

Hearing	Points	Definition
Full	0	No difficulty to hear ordinary conversation voice
Slightly decreased	1	Patient had some difficulty in hearing ordinary conversational voice
Moderately decreased	10	Patient occasionally asked what the examiner said although the latter spoke loud
Pronouncedly decreased	100	The patient found it very difficult to hear even when the examiner spoke very loud

Key 5

Bladder control	Points	Definition
Full	0	Full
Decreased	10	Occasionally incontinent or at most once a week
Pronouncedly decreased	100	Incontinent once a day or more often

examine and treat the patients with impaired communication not only for its own sake but also for rehabilitation in general.

Patients in whom cerebral function is so poor that they cannot cooperate properly can not be examined in the way described. Patients with dysphasia can not be properly examined according to the method described above for vision and hearing because the results would be more or less dominated by the dysphasia. In these cases the examiner judged the patient's ability to communicate also from his behaviour and from an interview with relatives or other people looking after him.

7—8 *Bladder and bowel control*

Bladder and bowel control was judged in the way illustrated in Keys 5 and 6.

Comments. Faecal incontinence is a much more serious handicap with a poorer prognosis than urinary incontinence (Peszczynski 1963, Levenson 1965), and the number of points was adjusted accordingly. Thus a patient with persistent pronouncedly decreased bowel control was given 1000 points and was judged as practically inaccessible to rehabilitation. Urinary or faecal incontinence indicates examination in order to find out whether the poor control of the bladder is due to some local factor, e.g. infection, spastic bladder, tumour etc. or whether faecal incontinence is due to rectal constipation, tumour etc. (Peszczynski 1963, Levenson 1965).

9 *Co-existing disease or symptoms*

Co-existing disease or symptoms is to be understood as a disease or symptoms not mentioned previously in this chapter. The following scale was used.

Key 6

Bowel control	Points	Definition
Full	0	Full
Decreased	100	Occasionally incontinent
Pronouncedly decreased	1000	Incontinent several times a week or more often

Key 3

Vision	Points	Definition
Full	0	Patient could read without difficulty
Slightly decreased	1	Patient could read with some difficulty
Moderately decreased	10	Patient could read only headlines and/or had hemianopsia
Pronouncedly decreased	100	The patient could not read headlines

adjust himself and learn to take care of himself and to walk (Peszczynski 1963) A hemiplegic with impaired vision usually requires examination by an ophthalmologist in order to find out whether vision can be improved by adequate treatment In the light of these observations the scale for vision was limited to the 100 point level

6) *Hearing*

Hearing was judged in the following way (Key 4)

Comments Impairment of hearing is common in elderly patients It can act as a barrier between the patient and his entourage to a degree varying with the severity of impairment of hearing A patient with impaired hearing usually requires examination by a specialist If hearing can be improved rehabilitation will be easier The scale was limited to the 100 point level

General comments on communication

Decreased ability to communicate must as far as disability is concerned, be viewed from two angles Firstly, it is disabling because it limits the patient s possibility to keep in touch with his entourage and may result in isolation of the individual Secondly, it makes rehabilitation more difficult since the latter requires active participation of the patient Rehabilitation is largely a learning process and communication between the patient and the instructor is necessary

It is therefore necessary to evaluate

Key 4

Hearing	Points	Definition
Full	0	No difficulty to hear ordinary conversation voice
Slightly decreased	1	Patient had some difficulty in hearing ordinary conversational voice
Moderately decreased	10	Patient occasionally asked what the examiner said although the latter spoke loud
Pronouncedly decreased	100	The patient found it very difficult to hear even when the examiner spoke very loud

subvariable at the 1 point level Group III has at least one subvariable at the 100 point level and at most 8 subvariables at the 100 point level with a subvariable at the 10 point level Group IV has at least one subvariable at the 1000 point level and at most three subvariables at the 1000 point level with six subvariables at the 100 point level As mentioned the scales of the respective subvariables vary according to their disabling effect The limits of the groups can therefore comprise a varying number of subvariables at different point levels

Group I consists of patients in whom the medical function is so slightly decreased that the patients could be expected to lead an ordinary life Group IV contains patients with pronouncedly decreased medical function Their sociomedical performance is expected to be pronouncedly decreased Between these extreme groups are groups II and III which are characterised by slightly respectively moderately decreased medical function In some of these patients the performance may be expected to be full or slightly to moderately decreased

If we place all 4 groups along the main variable A in our theoretical model (page 10) group I will be highest up group IV lowest and groups II respectively III between these extreme groups There is a certain range of variation within each group The patients in group II and III are most interesting from a point of view of rehabilitation and therefore they should be examined most carefully

Sociomedical performance

The main variable sociomedical performance comprises a number of subvariables which represent different types of performance at different levels and which place different demands on the patient from a functional point of view The subvariables are

1 Self care
2 Walking ability
3 Ability to travel
4 Household activity
5 Vocational activity

1 *Self care*

The evaluation of self care was based on the patient's ability to perform the following activities—subvariables—each of which consisted of three components namely

a) Eating Helping himself to food Cutting of food Lifting the food to the mouth

b) Dressing Dressing of underclothes with buttoning of *e g* jacket brassiere or corsette Putting on dress or suit and doing up of buttons Putting on stockings and shoes and doing up shoelaces

c) Personal hygiene Washing taking a bath or a shower Combing Using toilet

For each of the three subvariables *eating dressing and personal hygiene* the same number of points were given and the definitions used were as follows (Key 7)

Comments The three subvariables eating dressing and personal hygiene

Points	Definition
0	No disease
1	Co existing disease or symptoms which do not disable the patient or contraindicate rehabilitation
100	Co existing disease or symptoms increasing the disability of the pa tient but not contraindicating re habilitation
1000	Co existing disease or symptoms contraindicating rehabilitation

Comments Most hemiplegics belong to the higher age classes where diseases other than hemiplegia are also com mon Since any disease can later im pair the prognosis and decrease the patient s performance it was consid- ered justified to give 1 point for any co existing disease even if it had no disabling effect or in no way contra- indicated rehabilitation at the time of the examination Such diseases as in creased the disability of the patients were given 100 points This reflects the severity of the disease and at the same time indicates whether or not the disease is severe enough to interfere with rehabilitation In the usual way the patient should be examined to find out whether he can be improved by adequate treatment Diseases contra indicating rehabilitation are those which are severely disabling and in accessible to treatment those which make it impossible for the patient to cooperate at rehabilitation and those with a poor prognosis and short sur vival time This group was given 1000 points

Medical status groups

In clinical work with a given p it is the rule to collect various ob: tions to form an overall opinion patient's medical status and o basis of this to judge what socio cal performance might be expect the same way the subvariables of patient were taken together to fo point constellation According t appearance of this constellation entire material was divided into g called I, II, III and IV which ar fined according to the number of variables at the respective point l with the minimum and maximum its These groups were characte by decreased medical status acco to the numerical order I—IV The ciple is apparent from the follo list

Groups	Limits	Number of subvarial at respective levels			
		1000	100	10	1
I	Min	0	0	0	0
	Max	0	0	0	1
II	Min	0	0	0	2
	Max	0	0	7	1
III	Min	0	1	0	0
	Max	0	8	1	0
IV	Min	1	0	0	0
	Max	3	8	0	0

Medical status group I has at most subvariable at the level of 1 poi Group II has at least two subvariabl at the 1 point level and at most 7 su variables at the 10 point level with

Key 8

Walking ability on level ground	Points	Definition
Full	0	No walking difficulties
Slightly decreased	1	The patient had a limp or an unsteady gait and sometimes used a stick
Moderately decreased	10	The patient walked slowly and required a stick, crutches, trestles or the like
Pronouncedly decreased	1000	The patient could not walk without the aid of some person or not at all
Ability to ascend steps		
Full	0	No difficulties
Slightly decreased	1	The patient could ascend steps but only somewhat slowly
Moderately decreased	10	The patient could ascend steps but only very slowly
Pronouncedly decreased	1000	The patient could ascend steps only with the help of some other person or not even then

Group M has at least one and at most three subvariables at the 100 point level.

Group P has at least one and at most three subvariables at the 1000 point level.

This grouping was applied in the following example. A patient with slightly decreased ability to eat (10 points), moderately decreased ability to dress (100 points) and moderately decreased ability to manage personal hygiene (100 points) is given a point constellation of 210 for his self care and is assigned to performance group M. Another patient with slightly decreased ability to eat (10 points), pronouncedly decreased ability to dress (1000 points) and moderately decreased ability to manage his personal hygiene (100 points) will have a point constellation of *1110* and is assigned to performance group P.

2. Walking ability

Walking ability is to be understood as the patient's ability to walk on level ground and up steps. Every patient was also questioned as to the distance he thought he could walk, which is here called the "reported maximum possible walking distance". This is given as the approximate number of meters and was not allotted a number of points. Walking ability was classified in the following way (Key 8).

Comments. Walking ability is less complex than self care and its subvariables. It is necessary to grade the di

Key 7

Performance	Points	Definition
Full	0	Can perform all details
Slightly decreased	*10*	Can perform all details except one
Moderately decreased	100	Can perform all details except two
Pronouncedly decreased	1000	Can perform only one or no details

are necessary for an independent life The activities are complex and partly overlap Thus, the use of the toilet requires a certain ability to undress and dress However, a more detailed division of performance would be too artificial Patients who are not able to perform *any of the details described above are in need of personal aid The need* of personal aid was thus given *10* points Increasing number of points implies decreasing sociomedical performance and increasing need of help *The scale thus also shows to what ex*tent the patients need help This was done because these activities are basic and because it is important to analyse the cause of decreased function in detail *as well as the reasons for the need* of help in order to ascertain whether *the patient can by suitable measures* be made less, or completely independent

Successful rehabilitation regarding self-care has been reported by Licht (1949), Mahoney et al (1955), Lee et al (1958) and Lowenthal et al (1959)

By taking together the number of points for the subvariables eating dressing and personal hygiene, we get a *constellation* which expresses the level of the subvariable self care According to this constellation the material was divided into four groups full, slightly decreased, moderately decreased and pronouncedly decreased ability of the patients to take care of themselves *These groups are defined* according to the number of subvari*ables at the respective point levels with a maximum and minimum limits ac*cording *to the following* schema

Self care	Limits	Number of subvariables included by respective point levels			
		1000	*100*	*10*	*0*
Full (F)	Min	0	0	0	3
	Max	0	0	0	3
Slightly decreased (S)	*Min*	0	0	1	2
	Max	0	0	3	0
Moderately decreased (M)	Min	0	1	0	2
	Max	0	3	0	0
Pronouncedly decreased (P)	Min	1	0	0	2
	Max	3	0	0	0

Group F includes all subvariables at the 0 point level and patients with full ability to manage *self care*

Group S has at least one and at most three *subvariables* at the 10 point level

patient can himself decide the rate at which he works and he can rest when he is tired

Household activity depends on various factors besides working ability. Sex, civil status, what is expected of the patient and the patient's previous habits can play an important role. A certain difference in performance can also occur in one and the same activity group if a patient does not only his own household but also that of other persons.

a. Vocational activity

This applies to persons below 67 years, i.e. the age at which people are entitled to an old age pension (Michanec 1963). Housework at home is not included under the heading of vocational activity. The activity was classified in the following way:

Activity	Definition
Full (F)	Full employment in previous or other occupation
Decreased (D)	Part time employment
None (N)	No employment

Comments. Vocational activity depends not only on the patient's ability to work but also on several other factors, such as an opportunity to obtain suitable work, whether he has a superannuation, attitude of his entourage, dependants, if any, general economic situation etc.

General comments on sociomedical performance. Walking ability is the subvariable which can be most clearly isolated of the five subvariables of sociomedical performance. Self care includes several other kinds of activity, sometimes requiring complicated movements requiring good coordination and orientation. Ability to travel places larger demands on the patient than ability to walk and to manage self care. It also requires a higher level of cerebral function and vision, hearing and speech. Vocational activity is the most complex and places the largest demands on the individual, and as a rule presupposes—with a certain reservation for household activity—full or only slightly decreased performance regarding the other sociomedical subvariables, although a decreased ability to walk or to travel does not exclude vocational activity. Household activity at home is also complex, but often places less exacting claims on the individual than does vocational activity. All of the subvariables partly overlapped. The various subvariables of self care can be taken together under a common point constellation. To take together the point values for the other subvariables would, however, because of their nature mean a double representation which would result in an artificial decrease of the sociomedical performance. It is thus unsuitable to express the level of the variable sociomedical performance as a single point constellation. Instead the level of the single or partly combined subvariables, e.g. self care, were used in comparisons with those of medical status and psychosocial factors.

Key 9

Ability to travel	Points	Definition
Full	0	Without difficulty
Slightly decreased	1	The patient could travel with some difficulty
Moderately decreased	*100*	The patient could travel with a certain amount of personal help
Pronouncedly decreased	1000	The patient was entirely dependent on the company of some other person or the patient could not travel at all

crease of walking ability above the level of the necessity of living help which was given 1000 points The necessity of a stick or the like reflects the decrease of walking ability and the difficulties it means in various situations If a patient cannot walk without living help his walking ability is decreased to such an extent that further gradation is of little value

The striking possibilities of improving a patient's walking ability have been shown by Lee et al (1958) and Clausse et al (1963)

3 *Ability to travel* (tram bus etc)
Ability to travel was graded in the following way Key 9

Comments Ability to travel is more complex and places larger demands on the individual than the walking on level ground and up steps which details are also included in ability to travel The 100 point level means that the patient needs the help of some person for some details at the beginning of the journey or the end *e g* purchase of ticket, getting onto or off the tram or train or the like but otherwise he can manage to travel alone Ability to travel is necessary for those who are not working at home For those working at home or very close to their home ability to travel is less important But even for such patients ability to travel is important if the distance to the grocer s shop to the doctor, relatives etc , is long

4 *Household activity*
Household activity is to be understood as the actual light housework the patient does This subvariable consists of the following steps Preparing food Washing up Cleaning the house Making the bed It was graded as follows

Activity	Definition
Full (F)	*Does all details*
Decreased (D)	Does one or some details
None (N)	Does no details

Comments Since even healthy persons often hire help for heavy housework it was considered justified to limit household activity to include only light housework Such work often places less exacting demands on handicapped persons than vocational work for the

patient can himself decide the rate at which he works and he can rest when he is tired

Household activity depends on various factors besides working ability. Sex, civil status, what is expected of the patient and the patient's previous habits can play an important role. A certain difference in performance can also occur in one and the same activity group if a patient does not only his own household but also that of other persons.

a. Vocational activity

This applies to persons below 67 years, *i.e.* the age at which people are entitled to an old age pension (Michanec 1963). Housework at home is not included under the heading of vocational activity. The activity was classified in the following way:

Activity	Definition
Full F	Full employment in previous or other occupation
Decreased (D)	Part time employment
None N	No employment

Comments. Vocational activity depends not only on the patient's ability to work but also on several other factors such as an opportunity to obtain suitable work, whether he has a superannuation, attitude of his entourage, dependants if any, general economic situation etc.

General comments on sociomedical performance. Walking ability is the subvariable which can be most clearly isolated of the five subvariables of sociomedical performance. Self care includes several other kinds of activity, sometimes requiring complicated movements requiring good coordination and orientation. Ability to travel places larger demands on the patient than ability to walk and to manage self care. It also requires a higher level of cerebral function and vision, hearing and speech. Vocational activity is the most complex and places the largest demands on the individual and as a rule presupposes—with a certain reservation for household activity—full or only slightly decreased performance regarding the other sociomedical subvariables although a decreased ability to walk or to travel does not exclude vocational activity. Household activity at home is also complex, but often places less exacting claims on the individual than does vocational activity. All of the subvariables partly overlapped. The various subvariables of self care can be taken together under a common point constellation. To take together the point values for the other subvariables would however because of their nature mean a double representation which would result in an artificial decrease of the sociomedical performance. It is thus unsuitable to express the level of the variable sociomedical performance as a single point constellation. Instead the level of the single or partly combined subvariables, *e.g.* self care, were used in comparisons with those of medical status and psychosocial factors.

Key II

Ability to travel	Points	Definition
Full	0	Without difficulty
Slightly decreased	1	The patient could travel with some difficulty
Moderately decreased	100	The patient could travel with a certain amount of personal help
Pronouncedly decreased	1000	The patient was entirely dependent on the company of some other person or the patient could not travel at all

crease of walking ability above the level of the necessity of living help which was given 1000 points. The necessity of a stick or the like reflects the decrease of walking ability and the difficulties it means in various situations. If a patient cannot walk without living help his walking ability is decreased to such an extent that further gradation is of little value.

The striking possibilities of improving a patient's walking ability have been shown by Lee et al. (1958) and Claisse et al. (1963).

3. *Ability to travel* (train, bus, etc.)

Ability to travel was graded in the following way: Key II.

Comments: Ability to travel is more complex and places larger demands on the individual than the walking on level ground and up steps which details are also included in ability to travel. The 100 point level means that the patient needs the help of some person for some details at the beginning of the journey or the end, *e.g.* purchase of ticket, getting onto or off the tram or train or the like, but otherwise he can manage to travel alone. Ability to travel is necessary for those who are not working at home. For those working at home or very close to their home ability to travel is less important. But even for such patients ability to travel is important if the distance to the grocer's shop, to the doctor, relatives etc., is long.

4. *Household activity*

Household activity is to be understood as the actual light housework the patient does. This subvariable consists of the following steps: Preparing food, Washing up, Cleaning the house, Making the bed. It was graded as follows:

Activity	Definition
Full (F)	Does all details
Decreased (D)	Does one or some details
None (N)	Does no details

Comments: Since even healthy persons often hire help for heavy housework it was considered justified to limit household activity to include only light housework. Such work often places less exacting demands on handicapped persons than vocational work for the

et al (1962) Ullman (1962) and Rusk (1964) The accessibility of motivation to treatment has been stressed among others by Zane & Lowenthal (1960) Ullman (1962) and Rusk (1964) A pronouncedly decreased motivation requires special measures If motivation after a period of treatment is not improved psychiatric examination is indicated

2 Overprotection by relatives or people looking after the patient

Overprotective attitude is said to be present when persons around the patient are for some reason or other over helpful and may counteract or retard the patient s attempt to become independent

Evaluation of the occurrence or absence of overprotection is based on observations made during conversation with the patient and the relatives and at the clinical examination

Two degrees of overprotection may be recognised The results are given as + respectively — or when doubtful as ±

Comments The attitude of the hemiplegic s entourage is important for his activity and cooperation at rehabilitation (Ullman 1962 Davidson 1963 Rogoff et al 1964) If the patient s relative places adequate demands upon the patient s performance it can stimulate the patient to be more active If the relative overestimates the patient s disability or for some other reason gives him too much help the patient may become passive or completely dependent (Rankin 1957)

The reasons for overprotective attitude are many and often complex It is of importance to try to understand the background of overprotection so that treatment may be causal

3 Abode and family constellation

Type of home indicates whether the patient is living at home or at an institution and family constellation whether the patient is living alone or with others and if so whether with type of relative or with other persons sharing his home The following abbreviations were used

Home=H
Institution=I
Patient=P
Spouse=S
Child=C
Other relative=OR
Unrelated person=U

The symbol P without combination with some other abbreviation denotes that the patient is living alone Other combinations of these symbols indicate the composition of the family and with which other persons the patient may be living together The combination PSOR thus indicates that the patient shares his home with his or her spouse and some other relative though not a child which is always indicated by the symbol C

Comments The demands placed on patients varies with the type of abode Those living alone must usually perform more than those living with others who can often expect help from the persons they are living with The

Psychosocial factors

The psychosocial factors embrace a number of subvariables which may be of importance for the patient's socio medical performance and possibilities of improving it The variables differ widely from one another in character, therefore they must be described in different ways In the evaluation of hemiplegics the following questions are of importance What effect has the disease on the patient's social situation such as occupation, economic situation, family etc and how does he and his family experience their changed situation? What is the patient's general situation? What resources can be utilized in the planning of rehabilitation, e g regarding home, help and support of relatives etc? Adequate evaluation of the patient's performance and the possibilities of improving it must thus be seen against the background of the psychosocial factors Such psychosocial factors were selected as were thought to be able to influence the patient's performance

The subvariables are

1 Motivation
2 Overprotection by relatives or people looking after the patient
3 Abode and family constellation
4 Home help
5 Interior of home
6 Exterior of home
7 Economy

1 *Motivation*

One of the most important requirements for successful rehabilitation is active cooperation of the patient This depends, among other things, on the patient's motivation Evaluation of motivation is based on observations made when taking the patient's history, at the clinical examination and supplementary data obtained from relatives or people looking after him The following grades were applied

Motivation	Points
Full	0
Decreased	10
Pronouncedly decreased	1000

Comments Motivation is dependent partly on the patient's personality (Nadler & Shontz 1959) and can be influenced by previous or present environmental factors Psychological and social factors which may be of importance are the patient's opinion of himself, his situation, his disease his social role the attitude of his surroundings and what is expected of him the patient's knowledge of the possibilities of improvement of his performance and what possibilities of rehabilitation are available (Litman 1962)

The difficulty in measuring motivation has been pointed out among others by Rusk (1964) Sokolow et al (1958) used two levels while in 1962 they used three Gradation according to three levels allows a more detailed description of the patient's situation after which treatment can be adjusted The significance of motivation for the results of treatment has been emphasised by inter alia Rankin (1957) Lee et al (1958) Fisher (1961) Sokolow

room to himself which he should preferably have especially if he is bedridden or if he is no longer able to control his bladder or bowel while too large a home means unnecessary work

b) *Conveniences of home*

Modern conveniences are described by a number of subvariables which are important for hemiplegics Those conveniences lacking in the home are denoted by points the more important the lack of the convenience the higher the number of points

Lack of	Points
Garbage chute	1
Refrigerator	1
Electric stove	1
Running hot water	1
Bath or shower	10
Central heating	100
Indoor toilet	1000
Running cold water	1000
Drain	1000
Electricity	1000

By taking together the subvariables according to the number of points to a point constellation we get a general expression of the quality of the home as well as certain information on those facilities which are lacking On the basis of this point constellation the home was placed in one of 6 quality groups These are defined according to the number of subvariables within the respective point levels with minimum and maximum limits of each group according to the following schema

Quality groups	Limits	Number of subvariables within the various point levels				
		1000	100	10	1	0
I	Min	0	0	0	0	10
	Max	0	0	0	0	10
II	Min	0	0	0	1	9
	Max	0	0	0	4	6
III	Min	0	0	1	0	9
	Max	0	0	1	4	5
IV	Min	0	1	0	0	9
	Max	0	1	1	4	4
V	Min	1	0	0	0	9
	Max	1	1	1	4	3
VI	Min	2	0	0	0	8
	Max	4	1	1	4	0

The classification is based on the importance of certain facilities for the hemiplegic in his home such as bath or shower central heating indoor toilet etc

Quality group I has a point constellation 0 and none of the facilities listed are missing The point constellation of group II ranges from 1 to 4 this group lacks one or more of the facilities running hot water refrigerator electric stove and garbage chute The range for group III is 10 to 14 this group lacks a bath or shower and may in addition lack facilities at the 1 point level Group IV ranges from 100 to 114 and lacks central heating and may also lack other facilities at the 10 and 1 point level Group V ranges from 1000 to 1114 and lacks one of the facilities running cold water drain or electricity and may also have other deficiencies at the 100 10 and 1 point levels Group VI ranges from 2000 to 4114 and lacks two three or four of

expectations of help vary also with the degree of relationship between the patient and the person he is living with It is possible that a spouse will give more help than a distant relative or non relative The smallest demands are placed on patients living at institutions where the staff are responsible for all care

4 *Help in the home*

Help at home is accounted for partly by information as to how often help is given, partly by description of the person or persons helping the patient, *i e* whether a relative or non relative and if a relative the degree of relationship between the patient and the relative The same abbreviations were used as before in the description of the family constellation As to the frequency of help the following abbreviations were used

No help = —
1—2 times a month = M
1—3 times a week = W
Daily = D

Comments The help obtained by disabled persons is of interest from several points of view therefore a detailed description is justified No sharp line of distinction was drawn between help from a nurse and help with the household because the need for help is complicated and both types of help often overlap (Eltz 1963)

Home environments

An unsatisfactory home can considerably [re]duce the performance of persons who are disabled and increase their dependence on their entourage This may be due to lack of conveniences and modern equipment but also to unsuitable external circumstances Against this background it was considered justified to recognise two subvariables interior and exterior factors

5 *Interior factors*

The interior of the home included
a) Type of house and size of home
b) Conveniences
c) Telephone

a) *Type of house and size of home*

Type of house is to be understood as one family house, two family house or flat in a block of houses The size of the home is described as the number of rooms and kitchen and number of persons per room The last mentioned subvariable indicates whether the occupants are crowded The following abbreviations were used

One family house = 1 F
Two family house = 2 F
House block = B
One room and kitchen = 1 k
One room and kitchenette = 1 kT
One room and kitchen cupboard = 1 kC
Two rooms and kitchen = 2 k
etc

Comments Living in a detached house implies more work than living in a flat because then certain duties such as heating, cleaning of the staircase etc are taken care of by the owner of the house If the home is too small it may mean that the patient will not have a

room to himself which he should preferably have especially if he is bedridden or if he is no longer able to control his bladder or bowel while too large a home means unnecessary work

b) *Conveniences of home*

Modern conveniences are described by a number of subvariables which are important for hemiplegics Those conveniences lacking in the home are denoted by points the more important the lack of the convenience the higher the number of points

Lack of	Points
Garbage chute	1
Refrigerator	1
Electric stove	1
Running hot water	1
Bath or shower	10
Central heating	100
Indoor toilet	1000
Running cold water	1000
Drain	1000
Electricity	1000

By taking together the subvariables according to the number of points to a point constellation we get a general expression of the quality of the home as well as certain information on those facilities which are lacking On the basis of this point constellation the home was placed in one of 6 quality groups These are defined according to the number of subvariables within the respective point levels with minimum and maximum limits of each group according to the following schema

The classification is based on the

Quality groups	Limits	Number of subvariables within the various point levels				
		1000	100	10	1	0
I	Min	0	0	0	0	10
	Max	0	0	0	0	10
II	Min	0	0	0	1	9
	Max	0	0	0	4	6
III	Min	0	0	1	0	9
	Max	0	0	1	4	5
IV	Min	0	1	0	0	9
	Max	0	1	1	4	4
V	Min	1	0	0	0	9
	Max	1	1	1	4	3
VI	Min	2	0	0	0	8
	Max	4	1	1	4	0

importance of certain facilities for the hemiplegic in his home such as bath or shower central heating indoor toilet etc

Quality group I has a point constellation 0 and none of the facilities listed are missing The point constellation of group II ranges from 1 to 4 this group lacks one or more of the facilities running hot water refrigerator electric stove and garbage chute The range for group III is 10 to 14 this group lacks a bath or shower and may in addition lack facilities at the 1 point level Group IV ranges from 100 to 114 and lacks central heating and may also lack other facilities at the 10 and 1 point level Group V ranges from 1000 to 1114 and lacks one of the facilities running cold water drain or electricity and may also have other deficiencies at the 100 10 and 1 point levels Group VI ranges from 2000 to 4114 and lacks two three or four of

expectations of help vary also with the degree of relationship between the patient and the person he is living with. It is possible that a spouse will give more help than a distant relative or non relative. The smallest demands are placed on patients living at institutions where the staff are responsible for all care.

4 *Help in the home*

Help at home is accounted for partly by information as to how often help is given, partly by description of the person or persons helping the patient, i.e. whether a relative or non-relative and if a relative the degree of relationship between the patient and the relative. The same abbreviations were used as before in the description of the family constellation. As to the frequency of help the following abbreviations were used:

No help = —
1—2 times a month = M
1—3 times a week = W
Daily = D

Comments. The help obtained by disabled persons is of interest from several points of view; therefore a detailed description is justified. No sharp line of distinction was drawn between help from a nurse and help with the household because the need for help is complicated and both types of help often overlap (Litz 1963).

Home environments

An unsatisfactory home can considerably reduce the performance of persons who are disabled and increase their dependence on their entourage. This may be due to lack of conveniences and modern equipment but also to unsuitable external circumstances. Against this background it was considered justified to recognise two subvariables, interior and exterior factors.

5 *Interior factors*

The interior of the home included:
a) Type of house and size of home
b) Conveniences
c) Telephone

a) *Type of house and size of home*

Type of house is to be understood as one family house, two family house or flat in a block of houses. The size of the home is described as the number of rooms and kitchen and number of persons per room. The last mentioned subvariable indicates whether the occupants are crowded. The following abbreviations were used:

One family house = 1 F
Two family house = 2 F
House block = B
One room and kitchen = 1 K
One room and kitchenette = 1 KT
One room and kitchen cupboard = 1 KC
Two rooms and kitchen = 2 K
etc.

Comments. Living in a detached house implies more work than living in a flat because then certain duties such as heating, cleaning of the staircase etc. are taken care of by the owner of the house. If the home is too small it may mean that the patient will not have a

Comments The significance of unavoidable steps varies with the patient's ability to ascend them For patients who can walk on level ground but not up steps unavoidable steps may confine the patient to his home

b) *Distance to grocer's shop*

The distance to the next grocer's shop was described in the examiner's report as the approximate distance in meters This was compared with the reported maximum possible walking distance the patient said he could walk The distance to the grocer's shop was divided into the following groups

$<$ 300 metres
300—999 metres
$\geq$ 1000 metres

c) *Distance to neighbour*

The distance from the home to the nearest neighbour was described according to the same principles as distance to the grocer's shop though the limits for the groups were different For a patient to be able to reach his neighbour who is living in the same house or in the next house the walking ability should be at least 10 respectively 20 metres The distance was classified as follows

10—19 metres
20—49 metres
50—299 metres
$\geq$ 300 metres

[4] Support obtainable from state and community is surveyed in Social benefits in Sweden (1964)

Comments The ability to reach a grocer's shop or a neighbour may sometimes be of vital importance for a handicapped person If his walking ability is so impaired that he cannot manage the distance to the grocer's and if the groceries cannot be sent home to him he will be dependent on personal help If he cannot get in touch with his neighbour he will feel insecure with the result that his relatives may feel anxious and refuse to let him live alone

7 *Economy*

The patient's economic situation was investigated Information was obtained from the patient regarding his annual income capital old age pension superannuation or disability pension[4] any persons he had to support debts expenses for home home help medical help medicine etc Information was obtained from the local authorities regarding the total income of the patient and any financial[4] help given by the community

On the basis of this information the patient was said to be *in need of permanent economic support or not* Financial help was considered necessary if the patient had not any capital and if he was receiving regular help from a relative or from the community for everyday expenses If the patient was obviously in need of social help without however utilising this possibility he was said to be in need of economic help The patient was also asked whether he thought his economic situation was difficult or not Finally the patient's opinion and the results of the

the facilities at the 1000 point level and may also have deficiencies at the 1-, 10 and 100 point levels

Group I thus comprises homes with all the above mentioned conveniences group II, homes with relatively good conveniences, in groups III and IV certain fundamental conveniences are *missing*, and groups V and VI are very poor

The classification is illustrated by the following example A home with no indoor toilet (1000 points), central heating (100 points), bath or shower (10 points), running hot water (1 point) and garbage chute (1 point) will be given the number 1112 and is placed in quality group V

Comments In order to allow comparisons between the conveniences of the home and variables within medical status, e g function of leg, or socio-medical performance, e g household activity, a point constellation to serve as a ready expression of the quality of the patient's home was constructed

Experience has shown that a lack of certain combinations of conveniences is common This has been elucidated in 'Åldringsvard (S O U 1 1956), 'Åldringsvardens läge' (S O U 47 1963) and 'Pensionärshushall i fem städer (1964) In the first and last mentioned publications 4 qualities of living quarters were recognised, while in 'Åldringsvardens läge a more differentiated classification of 7 groups was recognised The content of the last-mentioned groups was in good agreement with the present method which, however, was constructed in such a way as to allow a certain variation in the respective quality groups

c) *Telephone*

The presence or absence of a telephone in the house was marked + respectively — It was not considered justified to give any points for the presence of absence of a telophone, because it does not belong to the fixed equipment of a house It is a tenant who decides whether he will have a telephone or not

Comments The use of a telephone for the hemiplegic means contact with the outer world, with relatives and friends and other services such as grocer's shop, hospital etc

6 *Exterior environment of home*

The subvariables are

a) Unavoidable steps at entrance
b) Distance to grocer s shop
c) Distance to neighbour

a) *Unavoidable steps to entrance of home*

The term 'Unavoidable steps at entrance is to be understood as steps which the subject must pass whether the steps are situated outside the house or, if he is living in a flat inside the house

Passage of steps was graded and given the points described below

Steps	Point
< 4 steps	0
To raised ground floor	10
To first floor or higher	100

Comments The significance of unavoidable steps varies with the patient's ability to ascend them. For patients who can walk on level ground but not up steps, unavoidable steps may confine the patient to his home.

b) *Distance to grocer's shop*

The distance to the next grocer's shop was described in the examiner's report as the approximate distance in meters. This was compared with the reported maximum possible walking distance the patient said he could walk. The distance to the grocer's shop was divided into the following groups:

$<$ 300 metres
300—999 metres
$\geqq$ 1000 metres

c) *Distance to neighbour*

The distance from the home to the nearest neighbour was described according to the same principles as distance to the grocer's shop though the limits for the groups were different. For a patient to be able to reach his neighbour who is living in the same house or in the next house the walking ability should be at least 10 respectively 20 metres. The distance was classified as follows:

10—19 metres
20—49 metres
50—299 metres
$\geqq$ 300 metres

[1] Support obtainable from state and community is surveyed in "Social benefits in Sweden" (1964).

Comments The ability to reach a grocer's shop or a neighbour may sometimes be of vital importance for a handicapped person. If his walking ability is so impaired that he cannot manage the distance to the grocer's and if the groceries cannot be sent home to him he will be dependent on personal help. If he cannot get in touch with his neighbour he will feel insecure with the result that his relatives may feel anxious and refuse to let him live alone.

7 *Economy*

The patient's economic situation was investigated. Information was obtained from the patient regarding his annual income, capital, old age pension, superannuation or disability pension[1], any persons he had to support, debts, expenses for home, home help, medical help, medicine etc. Information was obtained from the local authorities regarding the total income of the patient and any financial[1] help given by the community.

On the basis of this information the patient was said to be in need of permanent economic support or not. Financial help was considered necessary if the patient had not any capital and if he was receiving regular help from a relative or from the community for everyday expenses. If the patient was obviously in need of social help without, however, utilising this possibility, he was said to be in need of economic help. The patient was also asked whether he thought his economic situation was difficult or not. Finally the patient's opinion and the results of the

examiner's investigation of the patient's financial situation were compared

The results of the investigation of the patient's economy were expressed with the aid of three subvariables

a) Pension
b) *Economic problems reported by the patient*
c) *Need of economic support*

Affirmative and negative answers to questions in subvariables b) and c) were denoted by + respectively —

The following abbreviations were used for pensions

Old age=OA
Disability=D
Superannuation=S
None=N

Comments Evaluation of the importance of economic factors in the patient's performance and accessibility to rehabilitation requires knowledge of his financial position and the help he needs to cover his everyday expenses and secondly of the patient's personal opinion of his income in relation to his requirements The patients' pensions are important from different points of view and are therefore accounted for separately

Collection of data

A group of patients who within a 10 year period had been admitted to the Medical clinic Lasarettet Lund because of *hemiplegia* were selected for the investigation Data on the patients during their stay in hospital were obtained from the hospital records

Those who were still living in 1960 *were traced with the aid of the parish registers, from which information was also obtained about the deaths that* had occurred after the patients had *left hospital Those who were still* living were first contacted with a *simple questionnaire After they had* answered they were asked by letters *whether they would cooperate in an* interview and an examination and if so, what time would be convenient

All of the survivals were visited by the author and socionom Ulla Fredlund of the department of social and preventive medicine the University of Lund The patients were interviewed between April and September 1960

Supplementary anamnestic data were obtained and the patients were examined by the author At the same time the social worker interviewed the relatives or the people looking after the patient such as the help he needed the interior and exterior of the patient's home his financial situation etc and any particular problems the patient had The author then interviewed the relative or person looking after the subject while the social worker interviewed the patient concerning his social situation Finally the interior and exterior milieu were examined by the social worker and the author together At these interviews two questionnaires were used which were filled in during the interview and the examination One of the questionnaires was filled in by the author It

contained questions of mainly medical and sociomedical nature while the other which contained questions of mainly psychosocial type was filled in by the social worker The contents of the two questionnaires partly overlapped

Certain information such as ability to control the bladder and bowel to use the toilet or to travel could not be judged objectively and in these respects we had to rely on what the patient or his relatives reported In the collection of the data an attempt was made to make as clear a distinction as possible between the variables The primary data obtained by the examiners on each patient were discussed

Tables were set up from which relevant data on each patient were transferred to a main table (No 59 in appendix page 103) which includes demographic data the patient s position regarding the subvariables of the three main variables and the final evaluation of the accessibility of the patient to rehabilitation and the goals of such rehabilitation

Comments As mentioned above, the patients were examined by clinical methods which have certain advantages and disadvantages But for practical reasons no other methods can be used in such a field examination

CHAPTER II

Material

Total population

During the 10 year period 1949—1958 377 consecutive cases of hemiplegia because of cerebral vascular disease were cared for at the Medical clinic, Lasarettet, Lund.

All of the cases were admissions for the first attack of hemiplegia. Only those patients were accepted in whom the hemiplegia persisted and had been verified by the hospital doctor who had examined the patient on admission to hospital. Owing to the difficulties in making a causal diagnosis ("A classification and outline of cerebrovascular diseases" 1958, Dalsgaard Nielsen 1956) and since studies on the diagnosis are retrospective the entire group was classified as cerebrovascular disease with neurological deficit corresponding to hemiplegia.

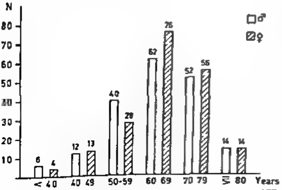

Fig 2 Sex and age distribution at onset of hemiplegia of 377 patients admitted in department of internal medicine between 1949 and 1958

The patients are classified according to sex and age at time of onset (Fig 2). The number of men (186) was practically the same as that of the women (191). The larger group (138) was between 60 and 69 years and the next largest (108) between 70 and 79 years. The youngest patient was 16 years and the oldest 82. The mean age of the men was 64.3 years and of the women 65.1 years.

The patients received conventional medical treatment without routine rehabilitation. The mean number of days in hospital was 32.7.

The mortality was highest in the acute stage. During the first month after the onset 32.6 % died, during the first year 51.2 % and during the two first years 62.8 %.

The examined group

At the examination in 1960 91 patients were still living. Fig 3 shows that the number of men (37) was smaller than that of the women (54). The largest group of men (17) were between 60 and 69 years and the largest group of women (26) between 70 and 79 years.

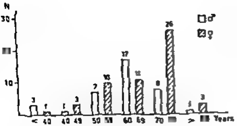

Fig 3 Sex and age distribution of 91 patients after-examined in 1960

The mean age of the men was 62 0 that of the women 66 2 years Fig 4 shows that equally many men (21) and women (24) were married while the number of previously married men (7) was much smaller than the number of previously married women (24)

Of the men (29) below 67 years at onset of disease most (26) had been in full employment and 2 in part time employment and 1 man had no occupation All (8) male old age pensioners could look after themselves and were independent of help

Of the females (39) who were below 67 years one fourth (9) had had a full time job or part time job (1) before the onset of their disease and three fourths had been fully (26) or partly (3) active in the household All (15) female old age pensioners were independent of help

The longest period that all were observed was 1 year and 4 months while the longest individual observation period was 11 years

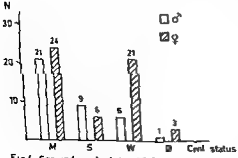

Fig 4 Sex and civil status of 91 patients after-examined in 1960

Recruitment of patients

The fact that the patients had been admitted to hospital implies that the material was to a certain extent selected Some patients with only slight symptoms never consult a doctor Some patients with slight symptoms are not referred to the hospital by their local doctors and some patients or their relatives refuse hospital care A small group die before transport to hospital The selection is dependent to a certain extent on the readiness with which doctors refer the patients to hospital Some patients are referred immediately to a home for chronic diseases Some patients are referred to other hospitals belonging to the same district Variation in the number of beds available from one time to another at Lasarettet Lund may also have influenced the principles for admission The increasing number of sub specialities at the Medical clinic may have resulted in certain decrease in the number of beds available for hemiplegics

During the period covered by the present investigation the receiving area of Lasarettet Lund has also varied owing to changes in the receiving areas of hospitals in Halsingborg and Angelholm i e hospitals serving areas bordering that catered for by Lasarettet Lund The distance between Halsingborg and Angel

holm is 28 km These towns are 54 and 69 km from Lund Because of the relatively long distances from these areas to Lasarettet Lund, it is however less likely that this should influence the admission of hemiplegics to Lasarettet Lund The hospital in Landskrona (32 km from Lund) opened up a medical department with 60 beds on January 1 1957 This may have resulted in slight changes in the admissions to Lasarettet Lund The sudden onset typical of hemiplegia usually leads to admission of the patient to the nearest hospital The increase in hospital facilities by the increased number of beds in Landskrona may thus have resulted in patients living between Lund and Landskrona being more often referred to Landskrona after 1957 Most of the reasons possibly influencing the admission to hospital apply also to other hospitals than Lasarettet Lund

Analysis of the places of abode of the patients who were admitted showed that these patients, as a rule, lived within or around Lund, rarely in the outskirts of the receiving area of Lasarettet, Lund and only exceptionally in other districts During the years 1949 to 1958 then the Medical clinic at Lasarettet, Lund, was the nearest one available for patients with hemiplegia

Comments It would thus appear that the present material was suitable for evaluating by the method described

CHAPTER III

Medical status of group examined

This chapter is concerned with the results of the examination of the patients' medical status or function in 1960. Accessibility to rehabilitation will also be touched upon. Each subvariable is described separately and such subvariables as may be expected to be interrelated are compared.

Paresis was rightsided in 40 patients (14 men and 26 women) and leftsided in 51 (23 men and 28 women). None had bilateral hemiplegia. Of the entire group one patient was lefthanded, all the others were righthanded.

During the observation period 14 patients (4 men and 10 women) had a recurrence with hemiplegia. Of these most (13) had one recurrence and one patient had two.

Function of arm and leg

Table 2 shows that function of the arm was full or slightly decreased in about half (48), moderately decreased in a few (8) and pronouncedly decreased in about one third (36). Function of the leg was full or slightly decreased in about half (49), moderately decreased in about one fourth (22) and pronouncedly decreased in equally many (20). On comparison between the function of the arm and of the leg, function of both limbs was full in one third (29), that of the arm was worse than that of the leg in about one third (26), that of the leg worse than that of the arm in one ninth (11), and function of the arm and that of the leg were decreased to the same extent in about one third (25).

Comments. Decreased function of the leg means that it is difficult for the patient to get about and thereby disables him more than the corresponding decrease of function of the arm (Lee et al. 1958). In two thirds (62)

Table 2. Function of arm and leg

	Arm				Total
Leg	0	1	10	100	
0	29	5	2	2	38
1	4	3	1	3	11
10	4	1	4	13	22
100	2	—	—	[illegible]	20
Total	39	[illegible]	7	[illegible]	91

Table 3 Cerebral function and function of arm

Function of arm	Cerebral function 0	10	1000	Total
0	24	12	3	39
1	5	4	—	[illegible]
10	2	2	3	7
100	10	7	19	36
Total	41	25	25	91

Table 4 Cerebral function and function of leg

Function of leg	Cerebral function 0	10	1000	Total
0	24	[illegible]	[illegible]	38
1	7	4	—	11
10	7	[illegible]	[illegible]	22
100	3	3	14	20
Total	41	25	25	91

function of the arm and/or leg was decreased Some of these patients appeared to be accessible to rehabilitation *This possibility depends on other* subvariables so that this group must be analysed further before anything definite can be said about their accessibility to rehabilitation

Cerebral function

Table 3 shows that about half (41) had full one fourth (25) decreased and one fourth (25) pronouncedly decreased cerebral function This decrease was most often thought to be due to the organic brain syndrome which was noted in more than half (14) of the patients with slightly decreased and in most (23) of those with pronouncedly decreased cerebral function *Other causes of decreased function* were anxiety neurosis depression etc In some cases the clinical picture was mixed with signs of *e g* anxiety neurosis and organic brain syndrome in the same patient In 4 patients organic brain damage was so pronounced *that in some respects the patients could* not cooperate satisfactorily at the examination

Comments About one fourth (25) of the entire group were thus little or not accessible to rehabilitation These patients should be examined further so that they might be given adequate treatment The poorest group probably required only general nursing care (*Smith et al 1960 Lamb et al 1963*)

Since *inter alia* the site and extent of the cerebral lesion can influence the relation between cerebral function and function of the arm respectively the leg these subvariables were compared Tables 3 and 4 show that of 41 patients with full cerebral function one fourth (12) had moderately or pronouncedly decreased function of the arm and equally many (10) moderately

or pronouncedly decreased function of the leg. Of 25 patients with pronouncedly decreased cerebral function four fifths (22) had moderately or pronouncedly decreased function of the arm and equally many (20) moderately or pronouncedly decreased function of the leg.

Comments. In many patients, then, pronouncedly decreased cerebral function occurred in association with moderately to pronouncedly decreased function of the arm respectively of the leg. One can thus hardly expect to produce any substantial improvement of such patients and therefore they do not lend themselves to advanced rehabilitation measures. The adequate type of treatment must be decided upon the basis of the other variables. However, combinations such as full cerebral function and moderately or pronouncedly decreased function of the arm and leg occurred. This group may be accessible to rehabilitation. In patients with pronouncedly decreased cerebral function and full function of the arm respectively leg the prospects of rehabilitation are probably decided mainly by cerebral function.

Communication

Speech

Table 5 shows that one fifth (19) had dysphasia. In most (16) it was expressive, in 2 it was mixed and in 1 it was global. None had dominantly impressive dysphasia. One fifth (4) of the patients with dysphasia had moderate and one fifth (4) pronounced dysphasia.

Since dysphasia makes it difficult to evaluate cerebral function, it is of interest to study the distribution of the patients in regard to these subvariables. Table 6 shows that of 72 patients without dysphasia three fifths (41) had decreased or pronouncedly decreased cerebral function. Of 19 patients with dysphasia half (9) had de-

Table 5. Type and degree of dysphasia

Degree	Type: E	E+I	G	Total
1	9	2	—	11
10	4	—	—	4
100	3	—	1	4
Total	16	2	1	19[1]

[1] In none was the dysphasia predominantly of impressive type.

Table 6. Dysphasia and cerebral function

Cerebral function	Dysphasia: 0	1	10	100	Total
0	31	6	3	1	41
10	21	3	1	—	25
1000	20	2	—	3	25
Total	72	11	4	4	91

creased or pronouncedly decreased cerebral function

Comments The results suggest that there is no covariation between the occurrence of dysphasia and decreased to pronouncedly decreased cerebral function A certain risk of underdiagnosis of dysphasia in patients with pronouncedly decreased cerebral function may be present If the cerebral function is so decreased that the patient cannot cooperate at the examination, dysphasia may remain concealed Of the 4 patients who had difficulties in cooperation at the examination 2 had dysphasia and 2 had not A possibly erroneous evaluation of the two last mentioned patients does not influence the conclusion of a probable absence of covariation between dysphasia and decreased cerebral function in this material nor does it influence the decision as to whether rehabilitation is indicated or not

Vision

Table 7 shows that vision was full in five sixths (77) Different degrees of impairment of vision were noted in one sixth (14) Pronounced decrease of vision was noted in 2 patients and 1 had hemianopsia

Of 41 patients with full cerebral function, one tenth (4) had decreased vision Of 50 patients with decreased or pronouncedly decreased cerebral function, one fifth (10) had decreased vision

Table 8 shows that of 72 patients without dysphasia one seventh (10) had decreased vision Of 19 patients with dysphasia one fifth (4) had decreased vision

Table 7 Vision and cerebral function

Cerebral function	Vision 0	1	10	100	Total
0	37	2	—	2	41
10	21	2	[illegible]	—	25
1000	19	5	1	—	25
Total	77	9	3	2	91

Table 8 Vision and dysphasia

Dysphasia	Vision 0	1	10	100	Total
0	62	6	2	2	72
1	9	1	1	—	11
10	2	2	—	—	4
100	4	—	—	—	4
Total	77	9	3	2	91

Comments According to table 7 there was a tendency of the patients with decreased to pronouncedly decreased cerebral function more often to have decreased vision than patients with cerebral function The result of examination of vision may be influenced by decreased cerebral function slowing

down the rate at which the patient understands the text held before him. This can result in overdiagnosis of slight impairment of vision in patients who have decreased cerebral function and both over- and underdiagnosis of decreased vision in patients with pronouncedly decreased cerebral function. However, these possible sources of error do not affect the decision whether the patient is accessible to rehabilitation or not.

Table [illegible] shows no certain covariation between dysphasia and decreased vision. Dysphasia can influence the result of examination of vision because what is registered as decreased vision may be entirely or partly due to expressive dysphasia or dyslexia. This applies above all to slight forms of dysphasia or dyslexia, which can lead to overdiagnosis of slightly decreased vision. In moderate or pronounced impressive dysphasia slightly to moderately decreased vision may remain concealed because of the decreased ability of the patient with dysphasia to read. As mentioned in the chapter on the method, in patients with dysphasia their behaviour and the reports of the people looking after them were used as a supplement in grading vision. The result of this variable, however, never excludes a patient from rehabilitation. More detailed diagnosis of these cases requires examination by an eye specialist and a specialist in dysphasia.

Hearing

It is clear from Table 9 that three fourths (66) had full hearing and that in about one fourth (25) hearing was impaired. In one third (9) of these hearing was moderately to pronouncedly impaired.

Table 9 Hearing and cerebral function

Cerebral function	Hearing				Total
	0	1	10	100	
0	31	[illegible]	1	—	41
10	17	5	2	1	25
1000	15	5	2	3	25
Total	66	16	5	4	91

Since decreased cerebral function can influence hearing because of impaired understanding of what is heard, these subvariables were studied for any covariation. Of 41 patients with full cerebral function hearing was decreased in one sixth (7). Of 50 patients with decreased or pronouncedly decreased cerebral function hearing was decreased in about one third (18).

Comments. Of the entire group then, one tenth had contact difficulties because of impaired hearing. The impairment was more common in patients with decreased to pronouncedly decreased than in those with normal cerebral function. The frequency was highest in patients with pronouncedly decreased cerebral function. The mean age of the patients with full cerebral function was 63.9 years. The corresponding age of the patients with pro-

creased or pronouncedly decreased cerebral function

Comments The results suggest that there is no covariation between the occurrence of dysphasia and decreased to pronouncedly decreased cerebral function A certain risk of underdiagnosis of dysphasia in patients with pronouncedly decreased cerebral function may be present If the cerebral function is so decreased that the patient cannot cooperate at the examination, dysphasia may remain concealed *Of the 4 patients who had difficulties* in cooperation at the examination, 2 had dysphasia and 2 had not A possibly erroneous evaluation of the two last mentioned patients does not influence the conclusion of a probable absence of covariation between dysphasia and decreased cerebral function in this material nor does it influence the decision as to whether rehabilitation is indicated or not

Vision

Table 7 shows that vision was full in five sixths (77) Different degrees of impairment of vision were noted in *one sixth (14) Pronounced decrease of* vision was noted in 2 patients and 1 had hemianopsia

Of 41 patients with full cerebral function, one tenth (4) had decreased vision *Of 50 patients* with decreased or pronouncedly decreased cerebral function, one fifth (10) had decreased vision

Table 8 shows that of 72 patients without *dysphasia one* seventh (10)

Table 7 Vision and cerebral function

Cerebral function	Vision 0	1	[illegible]	100	Total
0	37	2	—	2	41
10	21	2	[illegible]	—	25
1000	19	5	1	—	25
Total	77	[illegible]	3	2	91

Table 8 Vision and dysphasia

Dysphasia	Vision 0	1	10	100	Total
0	62	6	2	2	72
1	9	1	1	—	11
10	2	2	—	—	4
100	4	—	—	—	4
Total	77	9	3	2	91

had decreased vision Of 19 patients *with dysphasia, one fifth (4)* had decreased vision

Comments According to table 7 there was a tendency of the patients with decreased to pronouncedly decreased cerebral function more often to have decreased vision than patients with cerebral function *The result of examination* of vision may be influenced by decreased cerebral function slowing

Table 11 Co existing disease or symptoms graded according to score

Diagnoses or symptoms	1	100	1000	Total
Heart disease	6	16	—	22
High blood pressure	18	—	—	18
Epilepsy	—	5	—	5
Fractures	2	4	—	6
Miscellaneous	6	5	1	12
Total	32	30	1	63

Co existing diseases or symptoms

Other diseases and symptoms were noted in two thirds (63) The same patient often had several diseases besides hemiplegia In Table 11 each patient is given only one diagnosis the most important one Just as many belonged to the 1 point (32) as to the 100 point group (30) One patient who had a malignant inoperable neoplasm was given 1000 points

The following account is concerned with different diagnoses in the same patient so that the number of diagnoses is larger than the total number of patients with co existing diseases

Diseases of the heart were commonest and were noted in one fourth (24) Of these two thirds (16) had cardiosclerosis and one third (8) valvular heart disease mainly mitral stenosis Signs of incompensation were noted in one third (7) Of all the patients with heart disease one fourth (6) belonged to the 1 point group while three fourths (18) belonged to the 100 point group Some of the latter had slight incompensation enlargement of the heart or slight angina of effort The heart disease as such was never found to contraindicate rehabilitation in the present material In patients with pronounced incompensation of the heart however accessibility to rehabilitation is dependent largely on the prognosis of the heart disease and the goal of rehabilitation

The diastolic blood pressure was 105 or more (Master et al 1950 1958) in one third (27, 11 men and 16 women) The blood pressure was that noted at examination of the patient in his home and was therefore not equivalent to a diagnosis of hypertension The blood pressure was not judged as increasing the patient s disability or contraindicating rehabilitation and was given 1 point

In 5 patients epileptiform attacks occurred after the hemiplegia In 3 of the cases they were generalised and in 2 they were of Jacksonian type In all cases they were considered to increase the patient s disability Of 7 patients who had had a fracture of the lower limbs the fracture was of the femoral neck in 6 and of the femoral shaft in one In 4 patients the fracture increased the disability In the group of various diseases were 5 patients with diabetes mellitus 2 with disabling rheumatoid arthritis 1 with bronchial asthma which increased the patient s disability 2 with chronic renal disease and 1 with a malignant neoplasm in the region of the parotid

Comments Opinions on the hypertension as a prognostic factor in hemiplegia varies An unfavourable effect

Table 10 Hearing and dysphasia

Dysphasia	Hearing 0	1	10	100	Total
0	54	11	3	4	72
1	7	2	2	—	11
10	3	1	—	—	4
100	2	[illegible]	—	—	4
Total	66	16	5	4	91

nouncedly decreased cerebral function was 69 years This difference in age can probably not by itself explain the covariation between impairment of hearing and decreased cerebral function

Since the occurrence of dysphasia might influence the result of the examination of the patient s hearing *these subvariables were compared* Table 10 shows that of 72 patients without dysphasia one fourth (18) had *impairment of hearing and of 19 with* dysphasia hearing was impaired in one third (7)

Comments No definite covariation was found between impairment of hearing and dysphasia It is possible that dysphasia had caused an apparently high incidence of impairment of hearing Impaired understanding of the spoken word would, *for example be noted* by the examiner as impairment of hearing The risk is greatest in patients with slight impressive or slight mixed dysphasia *and slight impairment of hearing* On the other hand, slight impairment of hearing might remain concealed in patients with pronounced impressive dysphasia These sources of error, however, are of no practical significance in the evaluation of the indications for rehabilitation A more detailed analysis would require examination of hearing and speech by specialists

Ability to control the bladder and bowel

Decreased control of the bladder was noted in one tenth *(9)* Of these the control was slightly decreased in half (4) and pronouncedly in the remaining *(5)*

Decreased bowel control occurred in 5 In 4 of these the control was pro*nouncedly decreased*

Of the patients with decreased bladder control cerebral function was pro*nouncedly decreased in all except one* In all the patients with decreased bowel control cerebral function was *pronouncedly decreased and bladder* control was decreased

Comments A covariation was found between pronouncedly decreased bladder control and bowel control and pronouncedly decreased cerebral function *When local causes of this lack of* control of the bladder and/or bowel could be excluded the condition was taken as a manifestation of organic brain damage These patients are not accessible to rehabilitation (Rusk 1964)

Table 12 Distribution of patients according to level of subvariables and medical status groups

Scale	Arm	Leg	Cerebral	Speech (dysphasia) E	Speech (dysphasia) I	Speech (dysphasia) G	Vision	Hearing	Bladder	Bowel	Co existing disease or symptoms
	Medical status group I										
0	14	12	15	15	15	15	15	14	15	15	7
1	1	3		—	—		—	1			8
10	—	—	—	—			—	—	—		
100	—	—		—	—	—	—	—	—	—	—
1000			—							—	—
Total	15	15	15	15	15	15	15	15	15	15	15
	Medical status group II										
0	12	[illegible]	9	18	19	19	16	14	19	19	8
1	5	4		—	—		1	4			11
10	2	5	10	1			2	1	—		
100	—	—		—	—	—	—	—	—	—	—
1000			—							—	—
Total	19	19	[illegible]	19	19	19	19	19	19	19	19
	Medical status group III										
0	10	11	17	20	30	31	27	23	31	32	8
1	3	4		9	2		2	6			3
10	2	11	15	3			1	2	1		
100	17	[illegible]		—	—	1	2	1	—	—	21
1000			—							—	—
Total	32	32	32	[illegible]	32	32	32	32	32	32	32
	Medical status group IV										
[illegible]	3	5	—	20	25	25	19	15	17	20	6
1	—	—		2	—		5	5			10
10	3	6	—	—			1	[illegible]	3		
100	19	14		3	—	—	—	3	5	1	8
1000			25							4	1
Total	25	25	25	25	25	25	25	25	25	25	25

them the dysphasia was only slight Decreased vision was noted in one sixth (5) and impairment of hearing in one third (9) In two thirds (21) there were some other co existing disease which increased the patient s disability but did not contraindicate rehabilitation In most of the patients in this group sociomedical performance was expected to be decreased and some of them to be accessible to rehabilitation

In medical status group IV (25)

of hypertension has been reported by Rankin (1957), Marshall & Kaeser (1961) and Carter (1964), while Adams & McComb (1953) and Adams (1965) question whether hypertension really has an unfavourable effect in hemiplegia The favourable effect of hypotensive medicines has been stressed by Hood et al (1963), Marshall (1964), Aurell & Hood (1964) The necessity to treat patients with malignant hypertension is however, not questioned As for the present material, the value found on a single occasion at the patient's home was not considered sufficient to draw any prognostic conclusions or to say anything definite about contraindications of rehabilitation Patients in whom the diastolic blood pressure is persistently increased on repeated occasions should be investigated in the usual way and treated accordingly

Distribution of the subvariables among the various medical status groups

Table 12 shows the distribution of the medical subvariables in each of the medical status groups I II, III and IV Of the entire series group I comprised one sixth (15 4 men and 11 women) group II one sixth (19 4 men and 15 women) group III one third (32 17 men and 15 women) and group IV one third (25 12 men and 13 women) The intermediate groups II and III, in which the patients were expected to be accessible to rehabilitation consisted of more than half of the entire number of patients (51) The mean age of the patients in group I was 59 0 years, in group II 64 5 years, in group III 63 5 years and group IV 69 0 years There was thus a difference in age which was largest between groups I and IV

In medical status group I (15) the patients had entirely or almost entirely recovered In one fourth (4) function of the arm or the leg was slightly decreased Hearing was slightly decreased in one patient and half (8) had some other disease which not increased their disability or contraindicated rehabilitation The entire group may be expected to have full sociomedical performance

Of medical status group II (19), one third (7) had slightly to moderately decreased function of the arm and half (9) slightly to moderately decreased function of the leg Half (10) had decreased cerebral function Dysphasia was noted in one patient decreased vision in one sixth (3), while one fourth (5) had decreased hearing Half (11) also had some other disease which did not increase their disability In this group the sociomedical performance of some of these patients was expected to be decreased and some of them to be accessible to rehabilitation

In medical status group III (32) two thirds (22) had decreased function of the arm including 17 in whom it was pronouncedly decreased Function of the leg was decreased in two thirds (21), in half (11) of them it was moderately decreased and in one fourth (6) pronouncedly Cerebral function was decreased in half (15) Dysphasia was noted in half (15) In most (11) of

able for such a trial. Perusal of the literature showed as follows.

Improvement of hemiplegia which usually follows a characteristic course (Twitchell 1951, Hastings 1965) is quickest the first few weeks after the onset and afterwards decreases successively, and after 3—6 months becomes relatively stationary (Pincock 1957, Bard & Hirschberg 1965). Pincock's material which consisted of men with cerebral thrombosis was followed up for 8 years. Adams & McComb (1953) found that the patient's medical status and performance as a rule did not change during an observation between 0 months and 2 1/2 years.

In a rehabilitated selected series followed for [illegible] years Lee et al. (1958) found little deterioration in the patients' overall status and some other patients showed some decline in their abilities to carry out self-care, but those who were followed up personally showed little change in their employment status.

These results suggest that though this group differs partly from the other above mentioned series regarding composition and treatment given as well as regarding observation period, it lends itself to evaluation of the method described. The medical status can thus, apart from co-existing diseases, be regarded as relatively constant.

function of the arm was decreased in 22 and in most (19) of them it was pronouncedly decreased In four fifths (20) function of the leg was *decreased* and in most (14) of them it was pronouncedly decreased. The usual difference between the function of the arm and that of the leg *was thus not* demonstrable in this group and three fifths (14) had pronouncedly decreased function of *both* the arm and the leg In all 25 cerebral function was pronouncedly decreased Dysphasia was noted in one fifth (5) It was of expressive type in 3 Decreased vision *was noted in one fifth (6) and impair*ment of hearing in two fifths (10) In one third (8) there was decreased bladder control and in one fifth (5) decreased bowel control Diseases other *than hemiplegia were noted in four* fifths (19), in half (8) of whom the disease increased their disability and contraindicated rehabilitation in one The performance of the entire group was expected to be decreased and the patients were practically inaccessible to rehabilitation

On comparison between the distribution of the various subvariables within the various status groups there was an increased frequency of falling levels with increasing group number (I—IV) The distribution of some of the subvariables *e g function of the* arm and leg cerebral function control of the bladder and bowel and co existing diseases or symptoms, was characteristic

Group I was characterised by slight decrease of some single variable such as function of *the arm leg or co existing disease* Half of the patients in group II had *slightly to moderately de*creased function of the arm or leg and *decreased* cerebral function A few had slightly or moderately decreased ability to communicate All had normal bladder and bowel control Some other *co existing disease at the 1 point level was noted in half In group III* the number of patients with decreased function of the arm and leg became more and more striking Cerebral function was decreased Decreased ability to communicate was also *common* Only one patient had decreased bladder *control Some other co existing* disease which increased the patient s disability but did not contraindicate rehabilitation played an important role Group IV was characterised by *pronouncedly decreased function of* the arm and leg, pronouncedly decreased cerebral function and different degrees of impairment of communication and pronouncedly decreased bladder bowel control Co existing diseases at different levels occurred and in one case *contraindicated rehabilitation*

Comments The medical status groups give a rough impression of the medical status of the patients in the four groups This grouping will be used in the evaluation of the accessibility to *rehabilitation in Chapter V*

The range of severity of hemiplegia in the present material ranged from slight to pronounced The material was thus suitable for trying out the method On the other hand the observation period varied widely which might mean that the material was less suit

able for such a trial Perusal of the literature showed as follows

Improvement of hemiplegia which usually follows a characteristic course (Twitchell 1951 Hastings 1965) is quickest the first few weeks after the onset and afterwards decreases successively and after 3—6 months becomes relatively stationary (Pincock 1957 Bard & Hirschberg 1965) Pincock s material which consisted of men with cerebral thrombosis was followed up for 8 years Adams & McComb (1953) found that the patient s medical status and performance as a rule did not change during an observation between 9 months and 2 ½ years

In a rehabilitated selected series followed for 8 years Lee et al (1958) found little deterioration in the patients overall status and some other patients showed some decline in their abilities to carry out self care, but those who were followed up personally showed little change in their employment status

These results suggest that though this group differs partly from the other above mentioned series regarding composition and treatment given as well as regarding observation period it lends itself to evaluation of the method described The medical status can thus apart from co existing diseases be regarded as relatively constant

Sociomedical performance, medical status and psychosocial factors

Description and analysis of group examined

The results are given below according to the following scheme Each sociomedical subvariable is described separately First, the material is distributed according to one and the same subvariable This subvariable is then compared with the medical status, usually the subvariables, function of the leg respectively of the arm, cerebral function and co existing disease or symptoms This is followed by a presentation of such psychosocial factors as may be related to the sociomedical subvariable, and the interplay with the latter is elucidated Finally an account is given of the patients' socioeconomic situation

Self-care

The ability of the patients to eat dress and manage personal hygiene without help is given in Table 13

Table 13 Ability to eat dress and manage personal hygiene

Performance	Eating	Dressing	Pers hygiene
0	58	52	48
10	27	9	18
100	2	15	12
1000	4	15	13
Total	91	91	91

Two thirds (58) could eat without aid, one third (29) required personal help with one or two steps and a few (4) had to be fed Some of the patients in the intermediate group could manage their meals once the food had been cut into small pieces

About half (52) could dress themselves, one fourth (24) required help with one or two details, and one sixth (15) were practically entirely dependent on help Some of the patients could not lace their shoes themselves or fasten their cufflinks on the healthy side, or do up their brassiere etc

Half (48) could manage their personal hygiene while one third (30) required help with one or two details and one seventh (13) were entirely dependent on help Some of the patients could not get into or out of a bath without help

The patients tended to require more help with dressing than with the management of their personal hygiene

Table 14 Ability to manage personal hygiene and to dress

Dressing	Personal hygiene 0	10	100	1000	Total
0	48	3	1	—	52
10	—	7	1	1	9
100	—	8	6	1	15
1000	—	—	4	11	15
Total	48	18	[illegible]	13	91

Table 15 Ability to dress and eat

Eating	Dressing 0	10	100	1000	Total
0	40	4	5	—	58
10	3	4	10	10	27
100	—	—	—	2	2
1000	—	—	1	3	4
Total	[illegible]	8	16	15	91

(Table 14) The number requiring help with meals was smaller than that requiring help with dressing (Table 15).

Table 16 gives a scale for the subvariables ability to eat, dress and manage personal hygiene. The scores achieved for each of these activities are taken together as a measure of the patient to take care of himself (self

Table 16 Self care. Distribution according to performance and sex

	Performance[1] F	[illegible]	M	P	Total
♂	17	7	[illegible]	7	37
♀	29	6	9	10	54
Total	46	13	15	17	91

[1] Key to symbols and abbreviations is given on page 22

care). Half (46) of the patients could manage all three activities without help, one sixth (13) required help with at most one step, one sixth (15) with at most two steps and with two steps in one, two or three of the above subvariables, and one sixth (17) required help with practically all.

Comments. Half of the patients were dependent on daily help. It is probable that most of those who required only little help and possibly some of those who required moderate help could be taught to take care of themselves, particularly with the aid of specially constructed modern aids and conveniences.

Self care and medical status

Of 49 patients with full function or slightly decreased function of the leg one sixth (8) were slightly dependent on help (Table 17). Of 22 patients with moderately decreased function of the leg four fifths (17) were dependent

Table 17 *Self care and function of leg*

Function of leg	Self care F	S	M	P	Total
0	36	2	—	—	38
1	5	6	—	—	11
10	5	5	10	2	22
100	—	—	5	15	20
Total	46	13	15	17	91

Table 18 *Self care and function of arm*

Function of arm	Self care F	S	M	P	Total
0	35	2	2	—	39
1	7	2	—	—	9
10	1	3	2	1	7
100	3	6	11	16	36
Total	46	13	15	17	91

including 10 who were moderately dependent. When the function of the leg was pronouncedly decreased, help, sometimes considerable help was always necessary. Thus, in most of the patients who could not manage without help the function of the leg was moderately to pronouncedly decreased.

Table 19 *Self care and cerebral function*

Cerebral function	Self care F	S	M	P	Total
0	30	6	4	1	41
10	12	4	7	2	25
1000	4	3	4	14	25
Total	46	13	15	17	91

Table 18 suggests that severe reduction of the function of the arm was related to the ability of the patients to *manage without help less than was a* corresponding degree of reduction of the function of the leg.

Table 19 shows that of 25 patients with pronouncedly decreased cerebral *function, three fifths (14) required* considerable help. However the degree to which the patients with pronouncedly decreased cerebral function required help varied. Thus some of *those with pronouncedly decreased* cerebral function could manage with*out or with moderate help*. Analysis of these 11 cases showed that the function of the leg was often (10) not pronouncedly decreased.

Table 20 suggests a covariation between the occurrence of a co existing disease at 100 point level of the scale and decreased ability of the patients *to look after themselves*.

Comments Self care tended to vary with function of the leg. However

Table 20 Self care and co existing disease or symptoms

Co-existing disease or symptoms	Self care F	S	M	P	Total
0	17	5	5	2	29
1	18	4	4	6	32
100	11	4	6	8	29
1000	0	0	—	1	1
Total	46	13	15	17	91

some patients with full function or moderately decreased function of the leg could manage without help while others required help so that probably some other factors should be considered One of these factors is cerebral function Pronouncedly *decreased* function of the leg *combined with pronouncedly* decreased cerebral function implied the need of considerable help A few patients required no help despite pronouncedly decreased cerebral function This can probably be explained by the variation in the cause of the impairment of cerebral function and by the fact that in certain types of pronouncedly decreased cerebral function the patient is still able to take care of himself The tendency to covariation between co existing disease and self care suggests that even self care may be impaired by co existing disease at the 100 point level

Self care, medical status and psychosocial factors

a) Table 21 compares self care with *overall motivation* Owing to such a reduction of cerebral function motivation could not be judged in 5 patients (Nos 1 7, 47 76, 89) These patients were excluded from this analysis Half (47) of the patients had full motivation, in one third (32) it was decreased and in the remainder (7) it was pronouncedly decreased Of 47 patients with full motivation one third (14) required help and of 39 with decreased or pronouncedly decreased motivation two thirds (26) could not look after themselves It is thus possible that the decreased motivation might have contributed to decrease the ability of the patients to look after themselves in two thirds (26) of those requiring help Whether these are accessible to rehabilitation depends among other things on their cerebral function

Of 39 patients with decreased and pronouncedly decreased motivation a few (3) had full cerebral function

Table 21 Self-care and motivation

Motivation	Self care F	S	M	P	Total
0	33	7	7	—	47
10	12	5	6	9	32
1000	1	—	2	4	7
Total	46	12	15	13	86

Table 22 Motivation and cerebral function

Cerebral function	Motivation 0	10	1000	Total
0	38	3	—	41
10	9	12	3	24
1000	—	17	4	21
Total	47	32	7	86

Table 23 Motivation of patients living at home and overprotective attitude of relatives etc

Over protected	Motivation 0	10	1000	Total
Yes	3	10	3	16[1]
No	38	10	—	48
Uncertain	2	1	1	4
Total	43	21	4	68

[1] + 2 pat whose motivation could not be judged

while in one third (15) it was decreased and in half (21) it was pronouncedly decreased (Table 22) The last mentioned group was judged as practically inaccessable to rehabilitation Of the 18 remaining patients with decreased motivation half (9) required help Of these 2 (Nos 49, 87) could probably not be influenced regarding motivation Of the remaining 7 patients (Nos 48, 52, 61, 63, 71, 79, 88) motivation could probably be improved as a link in the process of rehabilitation

b) Evaluation of *overprotective attitude* of relatives or persons taking care of the patients was considered justified only regarding those 70 patients who were living at home It was considered too complicated to judge the institutionalised patients in this respect

Motivation can probably be impaired by overprotection of the patient Table 23 shows that such overprotection was noted in about 1/4th (18) In most (13) of them motivation was decreased Of 3/4ths not overprotected (48), motivation was reduced *in only* 1/5th (10) Of the above mentioned 7 patients requiring help and in whom motivation was regarded as reduced half (4) (Nos 48, 52, 61, 88) were overprotected *by the people taking care of them*

Comments Motivation was more commonly decreased among those who could not take care of themselves than among the remainder It was also more commonly decreased among *patients* who were overprotected Owing to the complex interplay between motivation and overprotection no attempts were made to analyse which of these two subvariables was the primary one The combined effect should *however* indicate the type of treatment necessary for the patient as well as instruction of the persons taking care of him

c) Table 24 shows that three fourths (29 men and 41 women) were *living at*

Table 24 Self-care and abode

Abode	Self care F ♂	F ♀	S ♂	S ♀	M ♂	M ♀	P ♂	P ♀	Total ♂	Total ♀
At home	[illegible]	29	4	5	5	[illegible]	4	2	29	41
At institution	1	—	3	1	1	4	3	8	8	13
Total	17	29	7	6	6	9	7	10	[illegible]	44
	46		13		15		17		91	

home and one fourth (8 men and 13 women) *at an institution*

Of those living at home half (34) were represented by patients belonging to medical status groups I and II while one third (26) belonged to group III and one sixth (10) to group IV

Most (18) of the institutionalised patients were at hospitals for chronic diseases two were living at an old age home and one at a mental hospital

Of the institutionalised patients one third (6) belonged to medical status group III and two thirds (15) to group IV None belonged to group I or II

Of the patients able to take care of themselves all except one were living *at home* while practically all of the institutionalised patients were dependent on help and half (11) of them required considerable help The number of women institutionalised was twice as high as that of the men The female predominance increased with the personal help required

However half (25) of those living at home *required help* and one fourth (6) of them considerable help The number of men (13) was just as large as that of the women (12)

Comments As expected the medical status was poorer and the need for personal help greater among the institutionalised patients than among those living at home Females were more common than males in the institutionalised group This difference in sex distribution may be due to some extent to greater difficulties for married disabled women living at home to obtain help than it is for married men because of the greater claims made on women than on men as nurses etc and the role played by men as bread winners with their working place usually away from home

d) Seven patients had no home for which reason this analysis was based on 84 patients Table 25 shows that one fourth (7 men and 12 women) of the series were *living alone* and three fourths (28 men and 37 women) *with others*

Of those living alone two thirds (13) could look after themselves and one

Table 25 Self care and living alone or with others

	Self care								Total	
	F		S		M		D			
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Alone	4	[illegible]	1	1	1	1	1	1	7	12
With others	13	20	4	5	5	7	6	5	28	37
Total	17	29	5	6	6	8	7	6	35	49
	46		11		14		13		84	

third (6) required help Of those living alone and able to look after themselves all except one were living at home, and of those who were dependent on help all except one (No 91) were living at an institution Of those living at home and able to take care of themselves women were more common but no definite difference in sex distribution was found among those patients who had been living alone and were now living at an institution

Of those living with others 33 could take care of themselves while 32 required help All of those in whom the ability to take care of themselves was not decreased and two thirds (24) of those requiring help were living at home The remaining patients (8) who were living with others were institutionalised Of those who were living at home, and able to take care of themselves the sex distribution was equal while men were more common among those requiring help

Comments The covariations between full ability of the patients to take care of themselves living alone and living at home are probably due to selection Those who were living alone and who required help had, as a rule been admitted to an institution In some though few, cases a patient living alone had moved to a relative Those who were dependent and living with others represented about one fourth of the entire material Thanks to daily help these patients could thus remain at home

e) The person giving help will vary with the *family constellation* at home Table 26 shows that two thirds (45) of those living with others were living with their spouse one eighth (8) with children and one fifth (12) with siblings parents or some unrelated person Most of the patients whose ability to take care of themselves was reduced and who were at home were living with their spouse (17) a few with their children (3) or some other relative or person (4)

f) Table 27 shows that three fifths (15) of the patients who were dependent received help from their spouse

Table 26 Self care and family constellation of patients living with relatives etc

Family constellation[1]	Self-care								Total
	F		S		M		P		
	♂	♀	♂	♀	♂	♀	♂	♀	
PS PSC PSOR PSL	11	14	2	4	4	[illegible]	4	1	45
PC PCOR PCL	—	3	1	—	—	2	—	2	8
POR PL	[illegible]	3	1	1	1	—	2	2	12
Total	13	20	4	5	5	7	6	[illegible]	[illegible]
	33		9		12		11		

[1] Key to symbols and abbreviations is given on page 27

Half (9) of them also received help of their children a relative or some other person Only one patient received help of children only the others (9) of some other relative or other person

Comments The daily help was usually given by the nearest relative living at home This was usually the spouse and rarely the children The above mentioned difference in sex was also noted regarding the person taking care of the patients who was usually a woman

g) Lack of modern *conveniences at home* probably decreased the patients ability to manage their personal hygiene but not their ability to dress or eat The subvariable personal hygiene was thus eliminated from the term self care and is accounted for separately in the comparison of the patients homes regarding conveniences

Table 28 shows that of all the patients (84) almost half (36) could not manage their personal hygiene The distribution of the patients able to manage their personal hygiene (33) was the same as that of those who required help (30) regarding group of home (I—IV) Of those living in less convenient homes (V—VI) on the other hand the number that was independent (15) was twice that of those dependent (6) on help Most of the independent patients were living at home irrespective of conveniences while one

Table 27 Self care and relatives or persons taking care of patients living at home

Cared for by [1]	Self care						Total
	S		M		P		
	♂	♀	♂	♀	♂	♀	
E	1	—	3	—	1	1	6
SC SOR SU	1	2	—	4	2	—	9
C COR	—	—	—	1	—	1	2
OR ORU	2	3	2	—	1	—	8
Total	4	5	5	5	4	2	25
	9		10		6		

[1] Key to symbols and abbreviations is given on page 27

fourth (8) of those depending on help and with homes of groups I—IV (30) and five sixths (5) of those dependent on help and with homes belonging to groups V—VI (6) were institutionalised

Since none of the homes were especially equipped to help the patients with hemiplegia to cope with their disability it is to be expected that even patients living in modern homes with all modern conveniences may have difficulties in managing their personal hygiene

All the patients living at home and with reduced ability to manage their personal hygiene (20) required help to take a bath They either found it difficult to get into or out of the bath because of decreased function of the leg and/or arm and by their anxiety which prevented them from trying to take a bath without help One patient (No 71) used a shower instead which she could manage without help All institutionalised patients except one required help with a bath Half (36) of the homes had no bath or shower

Table 28 Ability to manage personal hygiene and conveniences

Groups[1]	Personal hygiene 0	10	100	1000	Total
I	4	[illegible]	1	1	11
II	21	7	3	5	36
III	7	—	4	2	13
IV	1	1	1	—	3
V	11	3	—	1	15
VI	4	1	1	—	6
Total	48	17	10	9	84

Key to symbols and abbreviations is given on page 29

Of the patients with decreased ability to manage their personal hygiene one fourth (10) had not running hot water at home while 2 had not even running cold water In these 2 (Nos 10 and 80) who were institutionalised the function of the arm and/or leg was pronouncedly decreased and they would therefore have found it difficult to fetch water Of all the homes one third (28) had not running hot water and a few (6) had not even running cold water

None of the patients who could not manage their personal hygiene were without a drain in their home on the other hand the homes of two independent patients had no drain

One sixth (6) of the patients with reduced ability to manage their personal hygiene had no indoor toilet One of them (No 30) lived at home The other 5 patients were institutionalised Of these 3 (Nos 7, 10 80) because of their medical status could not walk to the toilet without help Of all the home one fourth (21) had no indoor toilet

Comments Most (5) of those dependent on the help of others and living in homes of the lowest category were institutionalised which suggests that the poor quality of the home might be one of the reasons for transferring a patient to an institution However 3 (Nos 10 30 80) of these 5 patients were living alone which is one of the primary factors to be considered in the evaluation of the requirement for institutional care of persons needing personal help The situation of the patients living alone and the group of home probably were contributory reasons for admitting them to an institution

The large number of patients who required help when taking a bath illustrates the inadequacy of conventional bathrooms for handicapped patients A slippery floor the absence of suitably placed handgrips the high wall of the bath slippery edges and curved slippery bottom of the bath all tend to increase the difficulties and risks of handicapped persons when getting into and out of a bath One patient had solved the problem by using a hand shower for washing which she could do without aid A suitable arrange

ment would probably be a shower with a rough, i e not slippery, floor and a permanent seat of the same type as in a wheeled toilet stool but without wheels and a hand shower with a long hose Such an arrangement would probably enable some of the patients to wash themselves without help Many of the homes had no bath or shower, which makes it difficult for the patients to manage their personal hygiene satisfactorily and increases the work of the people looking after them

The position of the bathroom is also of importance If it is situated in the cellar of a house without a lift, it cannot be used by patients with pronouncedly decreased ability to ascend or descend steps In 3 pensioners' homes in houses without a lift the bathroom was situated in the basement, which must surely be regarded as unsuitable

A large number of the patients who were unable to take care of themselves had no running hot water in their homes and some not even cold water This makes it difficult for them to manage their personal hygiene Boiling water for washing means that they must fill the kettle carry it to the stove and then pour it into a basin If they have no drain they must also pour the water out of the basin into a pail which they must then carry out of doors to empty it All this is very difficult for patients with walking difficulties and with only one serviceable hand and often necessitates the help of another person If they have no electric stove and if their home has only a coalstove or woodstove the procedure is still more laborious The patient must carry in wood and coal and make the fire

If there is no central heating and the home is heated by stoves or if the heating centre is situated in another storey than that in which the patient is living and the house is not heated with oil, it requires a large number of steps and a lot of work difficult for the hemiplegics to cope with These problems bear indirectly on the patient's ability to manage his personal hygiene

The situation of the toilet is also of importance for the patient's ability to manage his personal hygiene If it is situated outdoors, the patient must walk and, as a rule pass a few steps In winter, when it is cold and the ground is slippery, it is more difficult for the patient, besides which draughty outdoor toilets are far from inviting If an indoor toilet is not on the same floor as the patient's flat, it will also be difficult to use by a patient with difficulties to ascend and descend steps The lack of electricity means a further number of jobs, which usually require the use of two hands and a fair walking ability Only one home had no electricity

Owing to the seriousness of hemiplegia there is every reason to see that also patients who have recovered are given the opportunity to live in a home easy to manage

Walking ability

Table 29 shows that half (41) were able to walk on level ground In one

Table 29 Walking ability on level ground and function of leg

Function of leg	Walking ability 0	1	10	1000	Total
[illegible]	[illegible]	[illegible]	1	—	38
1	6	5	—	—	11
10	—		[illegible]	—	[illegible]
100	—	—	3	17	[illegible]
Total	41	14	19	17	91

Table 30 Walking ability on level ground and reported maximum possible walking distance

Reported max distance (metres)	Walking ability 0	1	10	1000	Total
>1000	31	[illegible]	2	—	39
300—900	4	3	[illegible]	—	9
[illegible]	[illegible]	4	8	[illegible]	20
0—49	—	1	7	15	[illegible]
Total	41	14	19	1	91

third (33) walking ability was slightly or moderately decreased and in one sixth ( ) it was pronouncedly decreased. Walking ability tended to vary with function of the leg.

It is clear from Table 30 that half (48) reported that they could walk more than 300 metres at a time, one fourth (20) between 50 and 299 metres and one fourth (23) less than 50 metres. The last mentioned group included also those who were bedridden.

Table 31 Ability to ascend and descend steps and function of leg

Function of leg	Walking ability [illegible]	1	10	1000	Total
0	33	4	1	0	38
1	5	[illegible]	—	—	11
10	—	[illegible]	11	9	[illegible]
100	—	—	—	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	20	91

Table 31 shows that half (38) of the patients could ascend steps while this ability was slightly to moderately decreased in one fourth (24) and pronouncedly decreased in one fourth (29). The ability to ascend steps varied with the function of the leg.

Ascending steps places larger demands on a patient with hemiplegia than does walking on level ground (Table 32).

Comments In a large proportion of the patients the ability to walk *on level ground and to ascend steps* was thus *reduced. It is probable that adequate* procedures could improve the walking ability of some of these patients with

ment would probably be a shower with a rough i e not slippery, floor and a permanent seat of the same type as in a wheeled toilet stool but without wheels and a hand shower with a long hose Such an arrangement would probably enable some of the patients to wash themselves without help Many of the homes had no bath or shower, which makes it difficult for the patients to manage their personal hygiene satisfactorily and increases the work of the people looking after them

The position of the bathroom is also of importance If it is situated in the cellar of a house without a lift, it can not be used by patients with pronouncedly decreased ability to ascend or descend steps In 3 pensioners' homes in houses without a lift the bathroom was situated in the basement, which must surely be regarded as unsuitable

A large number of the patients who were unable to take care of themselves had no running hot water in their homes and some not even cold water This makes it difficult for them to manage their personal hygiene Boiling water for washing means that they must fill the kettle carry it to the stove and then pour it into a basin If they have no drain they must also pour the water out of the basin into a pail which they must then carry out of doors to empty it All this is very difficult for patients with walking difficulties and with only one serviceable hand and often necessitates the help of another person If they have no electric stove and if their home has only a coalstove or woodstove the procedure is still more laborious The patient must carry in wood and coal and make the fire

If there is no central heating and the home is heated by stoves or if the heating centre is situated in another storey than that in which the patient is living and the house is not heated with oil, it requires a large number of steps and a lot of work difficult for the hemiplegics to cope with These problems bear indirectly on the patient s ability to manage his personal hygiene

The situation of the toilet is also of importance for the patient s ability to manage his personal hygiene If it is situated outdoors the patient must walk and, as a rule pass a few steps In winter when it is cold and the ground is slippery, it is more difficult for the patient besides which draughty outdoor toilets are far from inviting If an indoor toilet is not on the same floor as the patient s flat it will also be difficult to use by a patient with difficulties to ascend and descend steps The lack of electricity means a further number of jobs which usually require the use of two hands and a fair walking ability Only one home had no electricity

Owing to the seriousness of hemiplegia there is every reason to see that also patients who have recovered are given the opportunity to live in a home easy to manage

Walking ability

Table 29 shows that half (41) were able to walk on level ground In one

Table 34 Reported maximum possible walking distance and distance to nearest groucer s shop

Distance to groucer s shop (metres)	Max walking distance (metres)		Total
	>Distance to shop	<Distance to shop	
<300	35	13	48
300—999	8	11	[illegible]
≥1000	[illegible]	12	17
Total	48	36	84

3 and all 5 had to pass steps at the entrance of their homes In most cases the grocer s shop was at most 300 metres from their homes

About half (36) reported that they could not walk a distance corresponding to that to the grocer s shop In one third (13) of these the distance to the shop was less than 300 metres The medical status of those who reported that they could not go to the grocer s was as a rule poorer than that of those who said that they could Of the former group one third (13) were institutionalised compared with only one of the latter None of those living at home and unable to go to the grocer s shop were living by themselves

c) [illegible] is clear from Table 35 that three fourths (64) thought that they could manage to walk without help at least the *distance to their neighbour* Of these three fifths (38) had a neighbour in the same house and two fifths

Table 35 Reported maximum possible walking distance and distance to neighbour

Distance to neighbour (metres)	Max walking distance (metres)		Total
	>Distance to neighbour	<Distance to neighbour	
10—19	38	9	47
20—49	18	5	23
50—299	7	3	10
≥300	1	3	4
Total	64	20	[illegible]

(26) in another house usually (25) less than 300 metres away

Of those patients (20) who reported that the longest distance they could walk was less than that to their neighbour half (9) had a neighbour in the same house half (8) within 300 metres and the remaining (3) further away Of those who thought that they could not reach their neighbour one third (8) were living at an institution None of these 20 patients were living alone

Since there are usually several flats on the same floor or landing in large blocks of flats the ability to ascend steps was of minor importance for most of those who reported that they could walk for enough to *reach their* neighbour who was living in the same building as the patient

Of those whose neighbour lived in another house the possibility of a pa

Table 32 Ability to ascend and descend steps and to walk on level ground

Ability to walk	Ability to ascend steps 0	1	10	1000	Total
0	38	3	—	—	41
1	—	9	[illegible]	3	14
10	—	—	10	[illegible]	19
1000	—	—	—	*17*	*17*
Total	38	12	12	29	91

Table 33 Ability to ascend and descend steps and unavoidable steps to entrance of home

Unavoidable steps	Ability to ascend steps 0	1	10	1000	Total
0	14	[illegible]	[illegible]	[illegible]	29
10	12	4	5	10	31
100	12	3	1	8	24
Total	38	*12*	*11*	23	*84*

consequent improvement of a number of other sociomedical performances

When the reported walking distance was shorter than what might be expected *from the patient's walking* ability it was usually due to some coexisting disease (Table 30)

It is obvious from the typical somatic picture of hemiplegia with extensor contracture of the knee drop foot often combined with a tendency *to varus deviation, that it must be* more difficult for the patient to ascend steps than to walk on level ground If the strength of the hand grip is reduced, the patient cannot receive the support *otherwise offered by a hand* rail

Walking ability, medical status and psychosocial factors

a) Table 33 shows that of the patients (34) with moderately *(11)* or *pro*nouncedly decreased (23) ability to ascend steps, two thirds (24) had to ascend at least one flight of *steps to enter their home* Of these one fourth (6), all with pronouncedly decreased walking ability, were living at an institution Thus, one fourth (18) of those living at home found it difficult to go out because of unavoidable steps *they had to pass at the entrance of* their home Two thirds (12) of them required personal help

Comments Some of the patients with moderately decreased ability to walk on level ground but unable to ascend the unavoidable steps to enter their home could be made independent if their ability to manage steps could be improved or if they were *moved to* flats without steps at the entrance

b) Table 34 shows that about half (48) reported that they could walk a *distance* longer than that to the *nearest grocer s shop* Of these however ability to ascend steps was moderately *reduced in 2 pronouncedly decreased in*

Table 34 Reported maximum possible walking distance and distance to nearest grocer's shop

Distance to grocer's shop (metres)	Max walking distance (metres) >Distance to shop	<Distance to shop	Total
<300	35	13	48
300—999	8	11	19
≥1000	5	12	17
Total	48	36	84

3 and all 5 had to pass steps at the entrance of their homes In most cases the grocer's shop was at most 300 metres from their homes

About half (36) reported that they could not walk a distance corresponding to that to the grocer's shop In one third (13) of these the distance to the shop was less than 300 metres The medical status of those who reported that they could not go to the grocer's was as a rule poorer than that of those who said that they could Of the former group one third (13) were institutionalised compared with only one of the latter None of those living at home and unable to go to the grocer's shop were living by themselves

c) It is clear from Table 35 that three fourths (64) thought that they could manage to walk without help at least the *distance to their neighbour* Of these three fifths (38) had a neighbour in the same house and two fifths

Table 35 Reported maximum possible walking distance and distance to neighbour

Distance to neighbour (metres)	Max walking distance (metres) >Distance to neighbour	<Distance to neighbour	Total
10—19	38	9	47
20—49	18	5	23
50—299	7	3	10
≥300	1	3	4
Total	64	20	[illegible]

(26) in another house usually (25) less than 300 metres away

Of those patients (20) who reported that the longest distance they could walk was less than that to their neighbour half (9) had a neighbour in the same house half (8) within 300 metres and the remaining (3) further away Of those who thought that they could not reach their neighbour one third (8) were living at an institution None of these 20 patients were living alone

Since there are usually several flats on the same floor or landing in large blocks of flats the ability to ascend steps was of minor importance for most of those who reported that they could walk for enough to reach their neighbour who was living in the same building as the patient

Of those whose neighbour lived in another house the possibility of a pa

tient to visit a neighbour depended partly also on the presence or abscence of unavoidable steps and partly on his ability to ascend such steps Of the 26 patients mentioned the ability to ascend steps was decreased in 3, who had to pass steps to enter their homes

Comments Of patients living at home, one third (24) reported that they could not walk to the next grocer's shop and therefore required someone to do their shopping for them None of them were, however, living alone The distance to the shop was longer, and medical status poorer, in those cases where the patients said they could not walk to the shop

Of those who lived at home, one fifth (12) reported that they could not walk far enough to reach their neighbour None of them were living alone If such a patient is ever left alone or if the person taking care of him becomes ill it is impossible for him to reach his neighbour

d) Three fourths (61) of the patients had a *telephone* in their home and one fourth (23) had not (Table 36) Of those patients who reported that they were unable to walk to the grocer's shop 4 had no telophone in their homes Half (11) of the 23 patients without a telephone were, however allowed to use the telephone of a neighbour living in the same house Of those without a telephone walking on level ground was moderately or pronouncedly decreased in one third (9) Half (5) of them could thus not walk without help to his neighbour who had a telephone Of those who were living alone and had no telephone, 3 were living at home including one whose walking ability on level ground and up steps was moderately decreased

Table 36 Walking ability on level ground and telephone in home

Telephone	Walking ability 0	1	10	1000	Total
Yes	28	12	13	8	61
No	13	1	4	5	23
Total	41	13	17	13	84

Comments One fifth (15) of the patients living at home had no telephone In one fourth (4) of them walking ability was decreased, and one fifth (3) were living alone Those with a decreased ability to ascend steps are included in the group where the patients, owing to reduced walking ability on level ground found it difficult to use their neighbour's telephone

A telephone can break down the patient's feeling of isolation and increase his feeling of security and can make his daily life easier Even if a patient can walk to his neighbour and borrow the telephone there the lack of a telephone in his own home is a great inconvenience He may need a telephone to call a relative a nurse or a doctor at night or at other times less convenient to his neighbour or his neighbour may not be at home or busy

If a patient has a telephone in his

home it facilitates the work for his entourage If he cannot be left alone the people looking after him can get into immediate contact with various services etc If the patient has a telephone the people looking after him can leave him alone for a while in the knowledge that he can if necessary, get into touch with other people Friends and relatives living elsewhere can also keep in touch with the patient if he has a telephone As mentioned then a telephone breaks isolation and facilitates the care of the patients It would therefore appear desirable that all persons with hemiplegia have a telephone in their homes irrespective of their walking ability

Ability to travel

Less than half (40) of the patients were able to travel without aid (Table 37) One eighth (12) required some help and less than half (39) considerable help In most cases the ability to travel varied with the function of the leg In some however the ability to travel alone was reduced more than what might have been expected from the reduction of the leg function

The ability to travel alone also tended to vary with cerebral function (Table 38) Those patients with full cerebral function and need of company when travelling either had dysphasia impairment of vision or reduced function of the leg Those patients with decreased cerebral function and who required much help when travelling either had reduced function of the leg or some co existing disease

Table 37 Ability to travel and function of leg

Function of leg	Ability to travel 0	1	100	1000	Total
0	28	1	4	5	38
1	5	2	4	—	11
10	—	4	4	14	22
100	—	—	—	20	20
Total	33	7	12	39	91

Table 38 Ability to travel and cerebral function

Cerebral function	Ability to travel 0	1	100	1000	Total
0	24	4	5	8	41
10	9	2	3	11	25
1000	—	1	4	20	25
Total	33	7	12	39	91

In most of the patients in Table 37 in whom ability to travel was reduced more than expected cerebral function was pronouncedly reduced The others in this group had dysphasia, pronounced impairment of vision or some co-existing disease

Comments Reduced ability to travel was thus due to impairment of func

Table 39 Housework. Distribution according to performance and sex

	Performance[1] F	D	N	Total
♂	4	7	18	29
♀	22	16	3	41
Total	26	23	21	70

[1] Key to symbols and abbreviations is given on page 24

tion of the leg, of cerebral function, dysphasia, vision and certain co existing diseases

These results indicate what factors should be considered in the evaluation of indications for rehabilitation

More than half of the group required *company when travelling* This means limitation of the activity of some of these patients or a heavier burden for the people looking after them

Household activity

The analysis was based on 70 patients (29 men and 41 *women) who were not* living at institutions The extent to which the patients are expected to help in the housework varies at infirmaries and *homes for the aged because* any housework the patients do there is entirely voluntary Therefore no attempts were made to assess the household activity of *patients at institutions*

Table 39 shows that one third (26) were fully active one third (23) partly and one third (21) not at all

Of the men, one *tenth (4) were fully* active, while two thirds (18) did no housework Of the women, half (22) were fully active and one tenth (3) not at all

Comments As expected, marked differences with sex were noted at all *three levels* The men were less active throughout *than the women In those* where this could not be explained by differences in medical status it was probably ascribable to conventional *differences in the conception of the* division of duties with sex

Household activity and medical status

Of 45 patients with full or slightly decreased function of the leg one third (14, 7 men and 7 *women)* were partly active *in the household* and *one* sixth (7 men) were not active (Table 40) *Of* 17 patients in whom the function of the leg was moderately reduced half *(8 women)* were partly and half (7 5 men and 2 women) were not active Of those in whom the function of the leg was pronouncedly reduced practically *all were inactive in the household*

Table 41 shows that of 46 patients with full or slightly decreased function of the arm one third (15 6 men and 9 women) were *partly* *and one* sixth (7 men) were not active *Of* 19 patients with pronouncedly decreased function of the arm one *fourth (5 1 man* and *1* women) were partly and three fourths (13 10 men and 3 women) were not active

Of 38 patients *with full cerebral*

Table 40 Housework and function of leg

Function of leg	F ♂	F ♀	D ♂	D ♀	N ♂	N ♀	Total
0	3	16	6	6	5	—	36
1	1	4	1	1	2	—	9
10	—	2	—	8	5	2	17
100	—	—	—	1	6	1	8
Total	4	22	7	16	18	3	70
	26		23		21		

Table 41 Housework and function of arm

Function of arm	F ♂	F ♀	D ♂	D ♀	N ♂	N ♀	Total
0	2	16	6	8	5	—	37
1	1	5	—	1	2	—	9
10	—	1	—	3	1	—	5
100	1	—	1	4	10	3	19
Total	4	22	7	16	18	3	70
	26		23		21		

function one third (12 7 men and 5 women) were partly and one eighth (5 4 men and 1 women) were not active (Table 42) Of 22 patients with decreased cerebral function about half (9 women) were partly active and about half (8 7 men and 1 women) were inactive Of the 10 patients with pronouncedly decreased cerebral function 2 were partly and most (8 7 men and 1 woman) were not active

Table 43 suggests a tendency for de

Table 42 Housework and cerebral function

Cerebral function	Housework F ♂	F ♀	D ♂	D ♀	N ♂	N ♀	Total
0	4	17	7	5	4	1	38
10	—	5	—	9	7	1	22
1000	—	—	—	[illegible]	7	1	10
Total	4	22	7	16	18	3	70
	26		23		21		

Table 43 Housework and co existing disesase or symptoms

Co existing disease or symptoms	Housework F ♂	F ♀	D ♂	D ♀	N ♂	N ♀	Total
0	2	11	2	4	3	1	23
1	1	8	3	8	8	1	29
100	1	3	2	4	7	1	18
1000	—	—	—	—	—	—	—
Total	4	22	7	16	[illegible]	3	70
	26		23		21		

creased household activity to vary with the presence of co existing disease at the 100 point level

Comments The household activity of the patients tended to vary with the function of the leg and to a certain extent with the function of the arm Of the patients with pronouncedly decreased function of the arm however 1 was fully active and 5 partly active In other words these patients had learned to do all or some housework with one hand

Table 44 Housework and self care

Self care	Housework F ♂	♀	D ♂	♀	[illegible] ♂	♀	Total
I	4	21	6	8	[illegible]	—	45
[illegible]	—	1	1	1	3	—	9
[illegible]	—	—	—	4	5	1	[illegible]
P	—	—	—	—	4	2	6
Total	4	22	7	16	18	3	70
	26		23		21		

The household activity of the patients also tended to vary with the degree of cerebral function. Two women with pronouncedly decreased cerebral function could, however, do some housework but in these two the function of the arm or leg was not decreased. Their household activity could probably be explained partly by the fact that they had recovered from the hemiplegia and partly by the fact that the nature of the reduction of the cerebral function did not interfere with housework. Thus some patients with pronounced reduction of cerebral function may still be able to do routine work which they have been used to.

The 21 patients who were only partly active or inactive in the household despite full or slightly decreased function of the leg included some women with decreased cerebral function and men with full or decreased cerebral function and a few with moderately to pronouncedly reduced function of the arm, which agrees with the above mentioned conclusions that household activity tended to vary with cerebral function and with function of the arm. The previously mentioned difference with sex was obvious. The women did more housework than the men, even when their medical status was worse.

Household activity and self care

Of 45 patients who could manage their self care without help, more than half (4 men and 21 women) were fully active in the household, one third (6 men and 8 women) partly and one eighth (6 men) were inactive (Table 44).

Of the 19 patients in whom the ability to look after themselves was slightly or moderately decreased, half (1 man and 8 women) were partly active and half (8 men and 1 woman) were inactive. One woman in whom the ability

Table 42 Housework and cerebral function

Cerebral function	Housework F ♂	F ♀	D ♂	D ♀	N ♂	N ♀	Total
0	4	17	7	5	4	1	38
10	—	5	—	9	7	1	22
1000	—	—	—	2	7	1	10
Total	4	22	7	16	18	3	70
	26		23		21		

Table 43 Housework and co existing disease or symptoms

Co existing disease or symptoms	Housework F ♂	F ♀	D ♂	D ♀	N ♂	N ♀	Total
0	2	11	2	4	3	1	23
1	1	8	3	8	8	1	29
100	1	3	2	4	7	1	18
1000	—	—	—	—	—	—	—
Total	4	22	7	16	18	3	70
	26		23		21		

creased household activity to vary with the presence of co existing disease at the 100 point level

Comments The household activity of the patients tended to vary with the function of the leg and to a certain extent with the function of the arm Of the patients with pronouncedly decreased function of the arm however 1 was fully active and 5 partly active In other words these patients had learned to do all or some housework with one hand

Table 46 Housework and living alone or with others

	Housework						Total	
	F		H		N			
	♂	♀	♂	♀	♂	♀	♂	♀
Alone	2	9	1	2	—	—	3	11
With others	2	13	6	14	18	3	26	30
Total	4	22	7	16	18	3	29	41
	26		23		21		70	

household corresponded to their medical status and their decreased motivation made itself felt most regarding self care One patient (No 49) was inactive in the household mainly because of severe rheumatoid arthritis His motivation was pronouncedly decreased and was judged hardly improvable

In 2 (Nos 23 33) of the patients in whom household activity was decreased and 7 (Nos 3 5 12 38 45 59 68) who were not active in the household cerebral function was pronouncedly decreased and they were judged as hardly accessible to rehabilitation

Of those who did no housework the household of 4 men was managed by their wives or their landladies One (No 87) was a pensioner and was judged as firmly set in his situation Three patients (Nos 4 61 67) were in working age and should be encouraged to do occupational work

This thus left 7 patients 1 man and 6 women (Nos 42 48 53 65 73 79 88) in whom decreased motivation might have contributed to their decreased household activity Of these 5 (Nos 48 53 65 73 88) were *overprotected* by the people looking after them Judging from their medical status all of them could be expected to be fully active in the household except 2 (Nos 53 79) and even these could probably be expected to do more housework than they did

Comments The results suggest a covariation between decreased motivation and decreased housework Many of those patients whose household activity and motivation were decreased were also overprotected A factor tending to decrease activity in the household among men is the above mentioned conventional conception of the differences between the duties with sex especially if the entourage of the male hemiplegic do not expect him to do housework

b) Of 14 (3 men and 11 women) *living alone* most (2 men and 9 women) were fully active and *none* was inactive in the household (Table 46) Of 56 patients (26 men and 30 women) *living with others* barely one third

Table 45 Housework and motivation

Motivation	Housework						Total
	F		D		N		
	♂	♀	♂	♀	♂	♀	
0	3	21	6	6	6	1	43
10	1	1	1	8	9	1	21
1000	—	—	—	2	2	—	4
Total	4	22	7	16	17	2	68
	26		23		19		

to take care of herself was slightly decreased was fully active in the household.

All the patients who were markedly dependent on others for self care (4 men and 2 women) did no housework.

Comments Some of the women were active in the household though they were dependent on help for self-care. Most of the men were inactive in the household whether their ability to look after themselves was reduced or not. Thus, as mentioned above, the number of women active in the household was much larger than that of the men.

Household activity, medical status and psychosocial factors

a) In 2 of the patients (Nos 47, 76) the *motivation* could not be judged. The analysis was therefore confined to 68 cases.

There was full overall motivation in two thirds (43), which was reduced in one third (21) and pronouncedly reduced in a few (4) (Table 45). Of 43 patients with full motivation, one third (12: 6 men and 6 women) were partly active in the household, one sixth (7, 6 men and 1 woman) were inactive. Of 25 patients in whom motivation was moderately or pronouncedly decreased, barely half (11, 1 man and 10 women) did some housework and just as many (12: 11 men and 1 woman) did none.

Motivation was decreased in 2 patients who were fully active in the household. One (No 19) was living alone and did all her housework herself. For this patient housework was trying. The other patient (No 15) is discussed in the chapter on vocational activity.

Of the patients (42) who did some or no housework motivation was decreased in half (19) and pronouncedly in a few (4). As to these 23 patients the performance of two (Nos 52, 71) of the 19 who were partly active in the

Table 48 Housework and age

Age	Housework						Total	
	F		D		N			
	♂	♀	♂	♀	♂	♀	♂	♀
< 67 years	4	12	[illegible]	5	11	2	20	19
≥ 67 years	—	10	2	11	7	1	9	22
Total	4	22	7	16	18	3	29	41
	26		23		21		70	

active in the household 7 received help from their husbands 2 from the children and 6 from some other relative or employed person Five of the women who were partly active in the household received help from a woman employed by the community sometimes also help from a relative

In 1 (No 3) of the three women who were not active in the household the household was looked after by the husband The other 2 women were living with married daughters from whom they received help

Comments The help the patients received with the housework varied In some cases those giving help were persons serving both as nurses and charwomen In other cases the patients received help from a nurse and from a charwoman The patients decreased activity in the household often means a considerable burden to the relatives especially if they are out at work If the patients could be encouraged to do more housework themselves it would decrease the burden on the relatives and/or other persons

Even those who were fully active themselves required help with heavy chares

d) Table 18 shows that equally many men (20) as women (19) were *below 67 years* Among those who were fully active in the household women were predominant while men were predominant among those who were inactive Equally many men as women were partly active Nine of the men and 22 of the women were 67 *years or more* Of those partly active in the household women were more common and practically all of the males did no housework at all

Comments There was no clear difference between the household activity of the women below respectively above 67 years women thus continued their housework even after they had reached 67 years and despite decreased medical status

e) It is clear from Table 49 that the activity of the patients did not vary with the group to which their home belonged Since *lack of modern conveniences* in the home will probably

(15, 2 men and 13 women) were fully active, about one third (20, 6 men and 14 women) were partly active and about one third (21, 18 men and 3 women) were inactive in the household Most (11) of those living with others were living with their spouses and some (13) also with children some other relative or person Of the fully active patients 2 men and 3 women did not only their own housework but also that of another person

Comments Patients living alone differed clearly from those living with others regarding household activity Several of those living alone were fully active, while most of those living with others were only partly active or inactive This was probably due to several factors Those living alone consisted of a selected group whose medical status was better than that of many of those living with others Moreover those living alone had less housework to do because they only had to care for themselves But then again they could not get help from another member of the same household Those who were fully active and were living with others and did not only their own housework but also that for somebody else usually *have a heavier burden to carry* than those living alone Those partly active *in the household* and living with other people occupy a special position as far as housework is concerned in that they can usually get help from people whom they are living with As mentioned previously women were overrepresented among those active in the household

Table 47 Help by relatives or others

Help by [a]	Housework D ♂	Housework D ♀	Housework N ♂	Housework N ♀	Total
S	—	1	—	1	4
SC SU	—	4	—	—	4
C COR	—	2	—	2	4
OR U	1	6	1	—	8
Total	1	15	1	3	20
	16		4		

[a] Key to symbols and abbreviations is given on page 27

c) Table 47 shows the *persons who helped* those patients who did only part or none of the housework themselves Because of the larger claims made on women regarding housework all of the women are included in this analysis but only those men who were responsible for the household All together 20 patients (2 men and 18 women) were dependent on help with the housework One (No 6) was a man who did some of his housework and who received help from a woman employed by the community while the other one (No 12) did no housework and had a full time servant to do it for him

Of the 15 women who were partly

in 3 None of those without running cold water in their homes had to pass steps to reach the pump or well In one third (22) of the homes there was no running hot water and in a few (3) there was not even running cold water

Comments For those patients who had no refrigerator the prepurement of one would mean less frequent purchase of food and it would simplify the prepa ration of the food by providing better possibilities of keeping fresh and semi prepared food stuffs

A large group had no rubbish chute which means an increased walking distance on level ground than other wise and sometimes also the ascent of steps The patient must not only walk but also carry down the rubbish in a pail which may be difficult if he has only one serviceable arm and hand especially if he must use a stick when walking

Almost half of them had no electric stove An electric stove facilitates cook ing of the food and boiling of water It can be manipulated with one hand and the patient does not need to per form any precision movements other wise necessary for lighting the gas or a fire

Other difficulties in the preparation of a fire and the disadvantages of lack of central heating are discussed under the heading of self care A small group of homes had no running water and one had no drain The lack of these conveniences means increased diffi culties with a longer walking distance than otherwise and requires that the patient is able to carry heavy weights

Table 50 Vocational activity Distribution according to performance and sex

	Performance [1]			Total
	F	D	N	
♂	4	1	19	24
♀	2	2	19	23
Total	6	3	38	47

[1] Key to symbols and abbreviations is given on page 25

Proper conveniences would consid erably facilitate the life of hemiplegics

Vocational activity

This sections deal with 47 patients (24 men and 23 women) below 67 years

One fifth (9) were at work (Table 50) Of these 6 (4 men and 2 women) were fully active and 3 (1 man and 2 women) were partly active The ages ranged between 28 and 65 years with a median age of 52 0 years The me dian age of those who were not at work was 60 2 years

Of those at work 4 were manual labourers 4 had their own business and one was a white collar worker Those who were fully active included representatives of all three types of work while those who were partly ac tive were all persons working on their own account

One man had been promoted in the same branch and another had changed his occupation from that of a lorry driver to that of a welder The other

Table 49 Housework and conveniences

Groups[a]	Housework F ♂	F ♀	D ♂	D ♀	N ♂	N ♀	Total
I	1	2	1	3	2	—	[illegible]
II	1	8	2	9	11	2	33
III	1	5	—	1	2	1	10
IV	—	1	—	—	2	—	[illegible]
V	1	6	3	1	1	—	12
VI	—	—	1	2	—	—	3
Total	4	22	7	16	18	3	70
	26		23		21		

[a] Key to symbols and abbreviations is given on page 29

have its strongest effect on those who are partly active in the household, a special analysis was made of this group (23)

Of those who were partly active one sixth (4) had no refrigerator Of these, two (Nos 6, 65) could not walk to the grocer s shop One fifth (13) had no refrigerator in their homes

Of the homes of most of those who were partly active there was no rubbish chute in 17 Of these patients walking ability on level ground in one fourth (4) was moderately decreased and in one third (7) ability to ascend steps was moderately or pronouncedly decreased Of the last mentioned group most (5) had to pass steps to reach the dustbin Three fourths (55) of the patients had no rubbish chute in their homes

Of those who were partly active in the household, half (10) had no electric stove In half (4) of these patients function of the arm was moderately or pronouncedly decreased and in 2 walking ability on level ground was also moderately decreased Barely half (28) of them had no electric stove in their homes

Of those who were partly active in the household, one third (7) had not running hot water including 3 who had not running cold water either Of the above 7 patients function of the arm was moderately or pronouncedly decreased in 4 and walking ability on level ground was moderately decreased

in 8 None of those without running cold water in their homes had to pass steps to reach the pump or well In one third (22) of the homes there was no running hot water, and in a few (3) there was not even running cold water

Comments For those patients who had no refrigerator the prepurement of one would mean less frequent purchase of food and it would simplify the preparation of the food by providing better possibilities of keeping fresh and semi prepared food stuffs

A large group had no rubbish chute which means an increased walking distance on level ground than otherwise and sometimes also the ascent of steps The patient must not only walk but also carry down the rubbish in a pail which may be difficult if he has only one serviceable arm and hand especially if he must use a stick when walking

Almost half of them had no electric stove An electric stove facilitates cooking of the food and boiling of water It can be manipulated with one hand and the patient does not need to perform any precision movements otherwise necessary for lighting the gas or a fire

Other difficulties in the preparation of a fire and the disadvantages of lack of central heating are discussed under the heading of self care A small group of homes had no running water and one had no drain The lack of these conveniences means increased difficulties with a longer walking distance than otherwise and requires that the patient is able to carry heavy weights

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	Performance[1]			Total
	F	D	N	
♂	4	1	19	24
♀	2	2	19	23
Total	6	3	38	47

[1] Key to symbols and abbreviations is given on page 25

Proper conveniences would considerably facilitate the life of hemiplegics

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Of those at work 4 were manual labourers 4 had their own business and one was a white collar worker Those who were fully active included representatives of all three types of work while those who were partly active were all persons working on their own account

One man had been promoted in the same branch and another had changed his occupation from that of a lorry driver to that of a welder The other

Table 51 Vocational activity and function of leg

Function of leg	Vocational activity						Total
	F		D		N		
	♂	♀	♂	♀	♂	♀	
0	3	1	—	2	8	6	20
1	1	1	—	—	2	2	6
10	—	—	1	—	3	8	12
100	—	—	—	—	6	3	9
Total	4	2	1	2	19	19	47
	6		3		38		

7 had continued in their previous occupation The time these subjects had been unable to work, calculated from *the day of onset of the disease*, varied between 2 and 18 months with a median time of 9 0 months

Vocational activity and medical status

Since the number of subjects who were at work was small the discussion of the medical status will be based on the two groups *viz* vocationally active and inactive

Table 51 shows that of the 9 at work 6 *had full function of the leg* which was *slightly to moderately* decreased in the remaining 3 Of those who were *not vocationally active (38) the function of the leg was full* in one third (14), slightly *to moderately decreased* in one third *(15)* and pronouncedly decreased in one fourth (9)

Table 52 shows that of those who were active, *the function of the arm* was full in 6, slightly or pronouncedly decreased in the remaining 3 Of those who were inactive the function of the arm was full in one third *(14)* slightly *to moderately decreased in one sixth* (6) and pronouncedly decreased in half (18)

Of those who were active cerebral function was decreased in only one *(No 67) (Table 53) Of those who were* inactive cerebral function was full in one third (14) slightly decreased in just as many (14) and pronouncedly decreased in one fourth (10)

Most of those who were active had no co existing disease (6) while 2 women had co existing diseases not in*creasing* their disability and one man had a co existing disease which in*creased* his disability but did not contraindicate rehabilitation (Table 54) Of the inactive group *one third (13)*

Table 52 Vocational activity and function of arm

Function of arm	Vocational activity						Total
	F		D		N		
	♂	♀	♂	♀	♂	♀	
0	4	2	—	—	6	8	20
1	—	—	—	2	1	2	5
10	—	—	—	—	1	2	3
100	—	—	1	—	11	7	19
Total	4	2	1	2	19	19	47
	6		3		38		

Table 53 Vocational activity and cerebral function

Cerebral function	Vocational activity						Total
	F		D		N		
	♂	♀	♂	♀	♂	♀	
0	3	2	1	2	7	7	22
10	1	—	—	—	5	9	15
1000		—		—	7	3	10
Total	4	2	1	2	19	19	47
	6		3		38		

had some co-existing disease which did not increase their disability and one third (14) had some co-existing disease which did increase their disability but did not contraindicate rehabilitation.

Of the 38 inactive patients 7 (1 man and 6 women) did not only their own housework but also that of other persons. These 6 women had also been occupied mainly with their housework before the onset of hemiplegia. In most (5) of these women the *medical status* was only slightly decreased, e.g. slight *decrease of the function* of the arm

Table 54 Vocational activity and co existing disease or symptoms

Co existing disease or symptoms	Vocational activity F ♂	F ♀	D ♂	D ♀	N ♂	N ♀	Total
0	3	1	1	1	3	8	17
1	—	1	—	1	7	6	15
100	1	—	—	—	[illegible]	5	15
1000	—	—	—	—	—	—	—
Total	4	2	1	2	19	19	47
	6		3		38		

and/or leg, decreased cerebral function or some co existing disease at the 1-point level

Of the 31 *remaining persons* who were inactive the medical status in 25 men and women was as follows In 10 cerebral function was pronouncedly decreased, in another 4 the function of the leg was pronouncedly decreased, in a further 7 *the function* of the arm was pronouncedly decreased and in another 4 there was some coexisting disease at the 100 point level Combinations of the above decreases of function occurred in 13 of these patients *In these 25 patients their pronouncedly decreased medical status could explain* their vocational inactivity

Of the remaining 6 patients (3 men and 3 women), function of the leg was moderately decreased in 2 there was decreased cerebral function in 1 and *in the remaining* 3 the medical status was better than in the first 3 Most (2 men and 3 women) of these patients were active in the household either fully or partly, but none of them were *doing housework for other persons*

Comments The vocationally active patients were, as a rule younger than those who were inactive Of the former group males and females were equally common *In those who were occupationally active medical status* was usually only slightly impaired There was one exception (No 85) which will be discussed further in Chapter X

In a few of those patients who were vocationally inactive *their medical status* was also slightly decreased Most of them were women fully active in the household who looked after the household also for other persons and may *be regarded* as *vocationally active Another small group which differed* only slightly in medical status from that in which the women main

aged the household for another person had only their own housework to do or were partly active in the household There was also a larger vocationally inactive group in which the medical status was pronouncedly decreased and in which they did no housework Vocational activity or inactivity thus tended to vary with medical status The indications for vocational rehabilitation of inactive patients with slightly to moderately decreased medical status are discussed in Chapter V

Vocational activity and ability to travel

Of the vocationally active group, all patients (9) could travel alone In one (No 8a) ability to travel was slightly decreased In that patient the function of the right leg was moderately decreased and he had slight expressive dysphasia He was occupationally active at home Of those who were vocationally inactive in barely half (17) the ability to travel was at most slightly decreased and in about half (21) of them it was moderately to pronouncedly decreased

Comments In the vocational rehabilitation of patients training the ability to travel without aid is important

Vocational activity, medical status and psychosocial factors

a) In one (No 67) of the patients who was vocationally active *motivation* was decreased He had nevertheless undergone vocational training for another occupation In none of those who were partly active was motivation decreased

Of those who were not vocationally active motivation was decreased or pronouncedly decreased in more than half (18 11 men and 7 women) Of these 9 (6 men and 3 women) cerebral function was pronouncedly decreased which would prevent vocational employment In the remaining 5 men (Nos 4 15 53 61 81) decreased motivation was regarded as a contributory cause of vocational inactivity As to the remaining 4 women with decreased motivation vocational activity need not be considered

b) None of those who were fully or partially vocationally active were *overprotected* Of those who were not vocationally active one third (12, 6 men and 6 women) were overprotected In 3 cases (Nos 17 53 61) overprotection was regarded as a contributory cause of the patient s vocational inactivity

Comments Decreased motivation and overprotection were sometimes noted among vocationally inactive patients These results may serve as a guide in the analysis and occupational rehabilitation of hemiplegics

Economy

Table 55 shows that five sixths (76) of the patients were pensioners and that half (33) of these were receiving an old age pension and one third (28) a disability pension according to National Pension Scheme The remaining sixth (13) of the pensioners were re

Table 55 Type of pension and patient's opinion of economical situation

Economical problems	Type of pension[1] OA	D	S	N	Total
Yes	1	4	2	1	8
No	32	24	13	14	83
Total	33	28	15	15	91

[1] Key to symbols and abbreviations is given on page 32

ceiving a superannuation, mostly (12) besides one of the above mentioned pensions. Of those not receiving a pension (15) all except 2 had full-time or part time employment. One (No 62) who had no employment was on the sick list ('Social Benefits of Sweden' 1964) because of a recurrence of hemiplegia and one (No 81) had not availed himself of the opportunity to obtain a pension.

Table 55 also shows that in one tenth (8) of the entire material (Nos. 4, 16, 30, 61, 62, 68, 79, 88) *economic difficulties* were reported by the patients themselves or their relatives. All were pensioners except one (No 62) who was on the sick list. The problems reported were costs of keeping their children (Nos 4, 62, 88), home help (No 30), costs *for medicine and doctors* fees (Nos 68, 79), costs for upkeep of the house (No 16) and repayment of money he had borrowed so that he could enjoy a higher education (No 61).

Judging from an investigation of the patients' situation, 5 of them (Nos 4, 47, 61, 62, 68) were in need of regular economic help. In one (No 47) of these cases both the patient and his wife *denied economic difficulties*. They received regular economic help from their son.

Patient No 30 illustrates how economic factors can indirectly contribute to an increased activity. The patient was a 74 year old woman with pronouncedly decreased function of the arm and leg, who almost achieved *rehabilitation by herself*. *For one year* she had had daily help at home with the housework. Her husband gradually thought this too expensive. The wife therefore increased her household activity and could afterwards manage with a few hours' help a week.

A disability pension sometimes has an undesirable effect on attempted vocational rehabilitation of a patient. This is exemplified by the following illustrative case. The patient (No 36) was a 58 year old former swimming master who was living alone. At 47 years he had an attack of hemiplegia and had since then been receiving a *superannuation* and a *disability pension*. Already half a year after the onset the patient was practically independent despite pronouncedly decreased function of the arm. He led a secluded life. His pension was *about* 8 000 kr per annum which he found *quite enough to live on*. The fact that the patient was receiving a pension may explain why neither he nor the authorities thought of the possibilities of vocational rehabilitation. The patient was living in a *large town* where

it would surely have been possible for him to find some sort of occupation

Comments The economic situation varied widely from patient to patient in the group studied The data obtained would not allow any direct numerical comparison because of the wide variation of the patients ages capital occupations and dependents etc The patients were therefore simply divided into two groups according to whether they needed financial help or not Such a classification also served as a background to the evaluation of the patients conception of their economic situation Judging from the answers given by the patients at the interview only few thought their economic situation troublesome This can probably be explained by the State Insurance System in Sweden which entitles every citizen to an old age pension medical care and sick allowance in the event of illness and in the event of chronic disease a disability pension Though such financial support may normally be sufficient it may not be enough to allow the patient to cover certain expenses incurred by rehabilitation treatment *e g* journeys to and from a physiotherapeutist speech pedagogue etc which unlike journeys for medical consultation must be paid entirely by the patients For such rehabilitation some of the present patients would surely need economic help In addition economic difficulties may arise if the patients should permanently require the services of a nurse or of home help that cannot be given by the relatives or the community or if it should be necessary to reconstruct the flat or house because the allowances available for such necessities are limited

Economic factors can influence the patient s attitude to rehabilitation *e g* what economic advantages or disadvantages such rehabilitation involves A patient may thus have a negative attitude to vocational rehabilitation because it would deprive him of the feeling of safety his pension gives him especially if the occupation suggested *e g* a shielded job cannot be expected to give him an income substantially higher than his pension This problem has however been mitigated by the National Insurance Act according to which patients are allowed to receive part of their disability pension even when doing during part time employment as long as their working capacity is reduced

Table 55 Type of pension and patient's opinion of economical situation

Economical problems	Type of pension[1]				Total
	OA	D	S	N	
Yes	1	4	2	1	8
No	32	24	13	14	83
Total	33	28	15	15	91

[1] Key to symbols and abbreviations is given on page 32

ceiving a superannuation, mostly (12) besides one of the above mentioned pensions Of those not receiving a pension (15) all except 2 had full time or part time employment One (No 62) who had no employment was on the sick list ('Social Benefits of Sweden 1964) because of a recurrence of hemiplegia and one (No 81) had not availed himself of the opportunity to obtain a pension

Table 55 also shows that in one tenth (8) of the entire material (Nos 4, 16, 30 61, 62, 68, 79 88) economic difficulties were reported by the patients themselves or their relatives All were pensioners except one (No 62) who was on the sick list The problems reported were costs of keeping their children (Nos 4 62 88) home help (No 30), costs for medicine and doctors fees (Nos 68 79) costs for upkeep of the house (No 16) and repayment of money he had borrowed so that he could enjoy a higher education (No 61)

Judging from an investigation of the patients' situation, 5 of them (Nos 4 47, 61, 62, 68) were in need of regular economic help In one (No 47) of these cases both the patient and his wife denied economic difficulties They received regular economic help from their son

Patient No 30 illustrates how economic factors can indirectly contribute to an increased activity The patient was a 74 year old woman with pronouncedly decreased function of the arm and leg, who almost achieved rehabilitation by herself For one year she had had daily help at home with the housework Her husband gradually thought this too expensive The wife therefore increased her household activity and could afterwards manage with a few hours' help a week

A disability pension sometimes has an undesirable effect on attempted vocational rehabilitation of a patient This is exemplified by the following illustrative case The patient (No 36) was a 58 year old former swimming master who was living alone At 47 years he had an attack of hemiplegia and had since then been receiving a superannuation and a disability pension Already half a year after the onset the patient was practically independent despite pronouncedly decreased function of the arm He led a secluded life His pension was about 8,000 kr per annum which he found quite enough to live on The fact that the patient was receiving a pension may explain why neither he nor the authorities thought of the possibilities of vocational rehabilitation The patient was living in a large town where

it would surely have been possible for him to find some sort of occupation

Comments The economic situation varied widely from patient to patient in the group studied The data obtained would not allow any direct numerical comparison because of the wide variation of the patients ages, capital occupations and dependents etc The patients were therefore simply divided into two groups according to whether they needed financial help or not Such a classification also served as a background to the evaluation of the patients conception of their economic situation Judging from the answers given by the patients at the interview only few thought their economic situation troublesome This can probably be explained by the State Insurance System in Sweden which entitles every citizen to an old age pension medical care and sick allowance in the event of illness and in the event of chronic disease a disability pension Though such financial support may normally be sufficient it may not be enough to allow the patient to cover certain expenses incurred by rehabilitation treatment *e g* journeys to and from a physiotherapeutist speech pedagogue etc which unlike journeys for medical consultation must be paid entirely by the patients For such rehabilitation some of the present patients would surely need economic help In addition economic difficulties may arise if the patients should permanently require the services of a nurse or of home help that cannot be given by the relatives or the community or if it should be necessary to reconstruct the flat or house because the allowances available for such necessities are limited

Economic factors can influence the patient s attitude to rehabilitation *e g* what economic advantages or disadvantages such rehabilitation involves A patient may thus have a negative attitude to vocational rehabilitation because it would deprive him of the feeling of safety his pension gives him especially if the occupation suggested *e g* a shielded job cannot be expected to give him an income substantially higher than his pension This problem has however been mitigated by the National Insurance Act according to which patients are allowed to receive part of their disability pension even when doing during part time employment as long as their working capacity is reduced

Indications for rehabilitation

In the evaluation of the accessibility of a given patient to rehabilitation consideration must be given to his medical status and his sociomedical performance If his sociomedical performance corresponds to his medical status, the next step is to decide whether steps should be taken to improve his medical status and whether such improvement, if achieved, would improve his sociomedical performance If there is no such correspondence, the patient's psychosocial factors should be analysed, and in the event of any unfavourable factors it should be decided whether it is possible to correct such factors and whether such a correction could improve the patient's sociomedical performance In such an analysis it is advisable to judge the patient against the background of the goal of rehabilitation Attempts should be made to adjust the goal of rehabilitation to suit the patient's sociomedical performance with due consideration to his medical status and psychosocial factors after reasonable treatment and measures

The need for rehabilitation is described in what follows with three goals in mind, all of which are main basic activities necessary for an independent daily life and for the economy of the state These rehabilitation goals are self care, housework and vocational activity

Self-care

Table 56 shows that the ability of the patients to take care of themselves varies with their medical status However, of 46 patients who could manage without help, one fourth (12) belonged to medical status group III and one tenth (4) to group IV

Patients able to manage without help

Patients belonging to *medical status groups I and II* could, as expected, take care of themselves

Of the patients in medical status group III function of the leg was decreased in only one (No 73) Function of the arm was not decreased or only slightly decreased in most of them and was pronouncedly decreased in one (No 36) In none was cerebral function pronouncedly decreased Most of them had some co existing disease at the 100 point level which in this group did not affect the patient's ability to take care of themselves

One patient (No 36) was a 58 year

Table 56 Self care and medical status groups

Groups[1]	F ♂	F ♀	S ♂	S ♀	M ♂	M ♀	P ♂	P ♀	Total
	Self-care								
I	4	11	—	—	—	—	—	—	15
II	4	11	—	4	—	—	—	—	19
III	7	5	5	1	4	7	1	2	32
IV	2	2	2	1	2	2	6	8	25
Total	17	29	7	6	6	9	7	10	91
	46		13		15		17		

[1] Key to symbols and abbreviations is given on page 20

old former swimming master living alone His function of the right arm was pronouncedly decreased and he had slight expressive dysphasia His motivation was good and by intense training and ingenuity he had learned all the tricks necessary to manage his self care His home had all modern convenience

Of the 4 patients in *medical status group IV* three (Nos 2 23 33) had full function of the leg which was moderately decreased in one (No 68) cerebral function was pronouncedly decreased in all 4

Comments None of those who were able to take care of themselves had substantial walking difficulties In 3 of them function of the arm was pronouncedly decreased These 3 had learned to manage their self care with one hand Strangely enough 4 patients in whom cerebral function was pronouncedly decreased could manage their self care This was probably because the causes of pronouncedly decreased cerebral function are so many and different Moreover self care depends on basic activities which can sometimes be performed even when cerebral function is pronouncedly decreased

Patients with slightly decreased ability to manage self care

All 4 patients (Nos 21 26 79 91) in *medical status group II* found it difficult to get into and out of a bath and 2 (Nos 26 79) also required some help with their dressing such as fastening of hooks and eyes or lacing their shoes

Patient No 21 was a 43 year old woman in whom function of the left arm and leg was slightly decreased She had an exaggerated fear of falling and did not dare to get into or out of the bath without help She would be independent if she could be taught to overcome her fear, and if this did not *prove successful, her home should be* fitted with a suitable shower

In patient No 26 function of the right arm and leg was moderately decreased, but cerebral function and motivation were unimpaired Simple alterations of her clothing and replacement of the bath by a shower with a non slip floor would enable her to become independent

Patient No 79 was a 72 year old woman in whom function of the leg was slightly decreased, vision moderately decreased She was living together with her husband in a modern pensioner's flat The bath was of sitz-bath type with extra high walls, with the result that the patient had never used it since she had moved into the flat

The patient could be independent if *the bath were replaced by one with* lower walls or by a shower with a non-slip floor

Patient No 91 was an 83 year old woman who was judged as inaccessible to rehabilitation because of her poor general condition

Of the 6 patients in *medical status group III*, five (Nos 6, 35 71, 85, 87) required help to cut their food All of them could probably be taught to do so themselves In addition 4 (Nos 18 35, 71, 87) required help with small details of dressing One of them (No 87) did not dare to get into the bath without help It was thought that all 4 patients except one (No 87) could, by simple instruction and simplification of their clothing, be made independent as far as self care is concerned Patient No 87, a 68 year old man was very anxious and overprotected by his wife, so that it is doubtful whether he could ever become independent

Of the 3 patients (Nos 31, 47, 69) in *medical status group IV* probably none could be made independent owing to their decreased cerebral function One (No 69) of them might be taught how to cut his food, but he would probably still remain dependent regarding his personal hygiene

Patients with moderately decreased ability to manage self-care

Of the 11 patients in *medical status group III*, seven (Nos 17, 30 32, 48, 52, 61, 88) could probably be made independent The necessary measures var*ied and consisted of simple modifica*tions of the eating utensils such as the use of a fork with a sharp edge so that those patients with pronouncedly decreased function of the arm could learn to cut their food with one hand simplification of the clothing such as card strips instead of buttons, elastic ribbon instead of ordinary laces training various measures to improve their motivation, instruction of relatives how to induce them to modify their overprotecting attitude

Patient No 30 was a 74 year old woman living with others and with a pronouncedly decreased function of the right arm and leg and moderately decreased walking ability and she could not walk unaided to the outdoor toilet which was 25 metres from the house As a rule she therefore used a pail instead of the toilet but she could not empty the pail herself The patient needs an indoor toilet

One patient (No 61) differed from the rest At the time of the interview he had been sitting in a wheelchair for one month after having fallen and injured his left hip and he did not dare to seek medical aid because of an exaggerated fear of a recurrence of his hemiplegia His ability to take care of himself was decreased mainly by the hip injury which at later examination at the department of orthopaedics was found to be fracture of the femoral neck

Two patients (Nos 32 and 88) required help with a bath If they had had a shower with a non slip floor where they could take a shower sitting on a suitable chair they could be made independent

Of the remaining 4 patients two (Nos 29 41) could be made less dependent though not independent and two (Nos 57 80) were judged as unimprovable

Of the 4 patients (Nos 5 10 45 56) in *medical status group IV* three (Nos 5 45 56) could probably be taught to cut their food and thereby be independent at meals but otherwise they would probably have to remain moderately dependent regarding self care

Patients with pronouncedly decreased ability to manage self care

Of the 3 patients (Nos 49 63 76) in *medical status group III* two (Nos 63 76) were judged as accessible to rehabilitation

One (No 63) was a 78 year old woman with pronouncedly decreased function of the right arm and leg slight expressive dysphasia full cerebral function and decreased motivation She could probably learn to eat without help and should be trained to dress and manage her personal hygiene It is possible that this would grade her up to the group requiring only moderate help

The second patient (No 76) was a 66 year old woman with pronouncedly decreased function of the left arm and moderately decreased function of the left leg She showed signs of mental depression which should first receive treatment If treatment proved successful she could probably manage with less help and possibly become independent

None of the patients in *medical status group IV* were judged as accessible to rehabilitation Most of them were institutionalised (10) or so disabled (4 Nos 3 12 38 59) that they would have been institutionalised but for the generous help of their relatives

One patient No 38 was a 79 year old man with pronouncedly decreased function of the left arm and leg and pronouncedly decreased cerebral function. He was living together with his aged wife who could not give him all

Patient No 21 was a 43-year old woman in whom function of the left arm and leg was slightly decreased She had an exaggerated fear of falling and did not dare to get into or out of the bath without help She would be independent if she could be taught to overcome her fear, and if this did not prove successful, her home should be fitted with a suitable shower

In patient No 26 function of the right arm and leg was moderately decreased, but cerebral function and motivation were unimpaired Simple alterations of her clothing and replacement of the bath by a shower with a non slip floor would enable her to become independent

Patient No 79 was a 72 year old woman in whom function of the leg was slightly decreased, vision moderately decreased She was living together with her husband in a modern pensioner's flat The bath was of sitz bath type with extra high walls, with the result that the patient had never used it since she had moved into the flat

The patient could be independent if the bath were replaced by one with lower walls or by a shower with a non slip floor

Patient No 91 was an 83 year old woman who was judged as inaccessible to rehabilitation because of her poor general condition

Of the 6 patients in *medical status group III*, five (Nos 6 35, 71, 85, 87) required help to cut their food All of them could probably be taught to do so themselves In addition 4 (Nos 18 35, 71, 87) required help with small details of dressing One of them (No 87) did not dare to get into the bath without help It was thought that all 4 patients except one (No 87) could, by simple instruction and simplification of their clothing, be made independent as far as self-care is concerned Patient No 87, a 68-year old man was very anxious and overprotected by his wife so that it is doubtful whether he could ever become independent

Of the 3 patients (Nos 31, 47, 69) in *medical status group IV* probably none could be made independent owing to their decreased cerebral function One (No 69) of them might be taught how to cut his food, but he would probably still remain dependent regarding his personal hygiene

Patients with moderately decreased ability to manage self-care

Of the 11 patients in *medical status group III*, seven (Nos 17, 30, 32, 48, 52 61, 88) could probably be made independent The necessary measures varied and consisted of simple modifications of the eating utensils such as the use of a fork with a sharp edge so that those patients with pronouncedly decreased function of the arm could learn to cut their food with one hand simplification of the clothing such as card strips instead of buttons elastic ribbon instead of ordinary laces training various measures to improve their motivation, instruction of relatives how to induce them to modify their overprotecting attitude

Table 57 Housework and medical status groups

Groups[1]	Housework F ♂	♀	D ♂	♀	N ♂	♀	Total
I	1	10	3	1	—	—	15
II	1	9	—	6	3	—	19
III	2	3	4	7	8	2	26
IV	—	—	—	2	7	1	10
Total	4	22	7	16	18	3	70
	26		23		21		

[1] Key to symbols and abbreviations is given on page 20

the female patients because they are usually responsible for the care of the home and secondly for men who have taken over the role of the housewife e g living alone or with young children at home

Table 57 shows that most (21) of those active in the household (26) belonged to medical status groups I and II and that none belonged to group IV As to those who were partly active (23) were evenly distributed among all medical status groups Most (18) of the inactive (21) patients belonged to groups III and IV and none belonged to group I The women were more active in the household than the men in corresponding medical status groups Some of those doing some or no housework in groups I II and III could be expected to do more if adequate rehabilitation measures were taken

Full activity in household

Regarding both the man and the women belonging to *medical status group I* household activity was as expected

One patient (No 50) belonging to *medical status group II* was a 65 year old man living alone His household activity corresponded to his medical status

In 2 women (Nos 54 66) belonging to medical status group II function of the leg was moderately decreased and in this respect they differed from other women who were fully active in the household and in whom function of

the help he needed in their pensioner's flat on the second floor in a house without a lift The bathroom was situated in the basement Two married sons and one grandson lived in the same village as the patient One of the sons helped the patient out of the bed and dressed him every morning The grandson undressed the patient and helped him into bed every night, did his shopping and carried away rubbish from the flat A daughter in law did the washing for the patient, and his wife and another daughter in law cleaned the house Weather permitting, in summer the son and the grandson carried the patient down the steps and placed him on the luggage carrier of their cycle and pushed him to the son's allotment where he sat for a while in the open air

Comments Of the 45 patients dependent on help with self care, one third (15, 7 men and 8 women) could probably be made independent and the situation of a further one fifth (9, 4 men and 5 women) could be improved so that they could manage with less help but not be independent Of the 15 patients who could probably become independent 2 (Nos 14, 35) were living at an institution

The dependent patients who were judged as being accessible to rehabilitation showed some of the following characteristics full, to pronouncedly decreased, function of the arm slightly to moderately decreased function of the leg, full, to decreased cerebral function, full to pronouncedly decreased motivation Overprotection was noted in some of the cases

The rehabilitation measures required were *inter alia* as follows physiotherapy (in most patients), training and instruction to eat without help (15 patients), to dress (13 patients) and to manage their personal hygiene (11 patients) Attempts should be made to improve motivation in 8 and to induce the relatives to be less protective in 6 cases Advanced care at rehabilitation centre was considered indicated in 9 cases The coexisting diseases were, as a rule receiving treatment The homes should be improved in 8 cases

It was remarkable that none of the patients living at home had a wheel chair to use indoors The ability to move about without help is very important, not only for self care There is thus a possibility to train patients with pronouncedly decreased walking ability but in whom cerebral function is not pronouncedly decreased that they can learn to get in and out of a wheel chair and use it When considering whether the patient should be given a wheel chair the risk must however, be borne in mind that the patient might get accustomed to physical passiveness and cease to try to learn how to walk The use of a wheel chair also requires certain changes in the home e g removal of thresholds between rooms, etc

Household activity

Ability to do housework as a goal of rehabilitation is mainly of interest for

to a flat on the ground floor she would be able to go out

Of the other women in group II three (Nos 42 65 72) were judged as able to become fully active in the household and two (Nos 26 79) could probably do more work in the household but not become entirely independent

One patient (No 65) was a 57 year old woman who lived in the country together with her children and husband who was out at work. She had full function of the right arm moderately decreased function of the right leg and decreased cerebral function. Her motivation was decreased and she was overprotected by her husband. Her husband had heavy work as a farm labourer. The home was very poor and it had no running cold water no indoor toilet no central heating no electric stove no refrigerator and no rubbish chute. Attempts should be made to improve the patient's motivation, the patient should be trained to do full housework and the husband should be informed of the importance of stimulating the patient to work. The home should be equipped with modern conveniences which would markedly facilitate the care of the house

One patient (No 6) in *medical status group III* was a 56 year old widower who was living together with his 18 year son who was out at work. Function of the right arm was pronouncedly decreased, that of the right leg slightly. He had full cerebral function and moderate expressive dysphasia. The house had *no indoor toilet* no central heating, running hot water, refrigerator or rubbish chute. A woman paid by the community prepared the patient's food and cleaned the house. It was thought that the patient could learn to do this work himself but it would require training at a rehabilitation centre. A home with all modern conveniences would considerably decrease his degree of dependence

Patient No 53 was judged as being able to do more household work but probably not become fully active. His home was very simple and had no modern conveniences

Patients Nos 27 and 74 in group III helped their wives with the housework. There was no reason to try to increase the household activity of these two patients

Of the female patients *in medical status group III* the household activity of three (Nos 13 52 71) *corresponded* to their medical status

Patient No 30 in *group III* was a 74 year old woman living together with her husband who was out at work. The function of her right arm and leg was pronouncedly decreased and she had slight dysphasia. Her motivation was strikingly good. Her home had no *indoor toilet* no running warm water and no rubbish chute. The patient's activity in the household could probably be increased by training at a rehabilitation centre and after improvement of the home and equipment of the kitchen with technical aids for one armed persons. But she could presumably never become fully active

Of the *remaining* 3 patients in medical status group III two (Nos 48 and 89) were judged as being able to be

the leg was at most slightly decreased

One patient (No 66) was a 65 year old widow with *full function of the* left arm, with moderately decreased function of the leg, full cerebral function and full motivation She lived in an attic flat and had to ascend a steep flight of *stairs to reach it The flat had* no indoor toilet, no central heating no running hot water, no bathroom, no electric stove and no rubbish chute Despite moderately decreased walking ability *on level ground and up steps,* she managed her household alone Her married daughter helped her twice a week with heavy housework and with the shopping This woman required a *flat with modern conveniences* and without any steps at the entrance, which would mean a great improvement in the situation of this woman not only regarding her household work

One patient (No 15) belonging to medical status group III was a 24 year old man with full function of the arm and leg and with congenital heart disease without signs of incompensation He lived with his *parents and did the* housework for the family during those periods the mother was out working

One patient (No 36) was a 58 year man living alone The function of the right arm was *pronouncedly* decreased but he had full function of the right leg full cerebral function and full motivation His home had all modern conveniences The patient managed all the housework including heavy jobs without help

The three women (*Nos 19 55 84) in* group III had some co existing disease which placed them in this group of medical status Despite the co existing disease they were fully active in the *household*

Decreased activity in household

Two *(Nos 24, 28)* of the men in *medical status group I* helped their wives in the home to an extent corresponding to their medical status age and psychosocial factors No measures *were considered indicated*

One patient (No 14) in group I was a 60 year old widower living by himself He had recovered entirely from his hemiplegia His married daughter *helped him with the household* It is possible that he could manage the housework himself although his age previous habits and lack of experience with housework would make it some*what difficult*

Of the women in group I the household activity of one patient (No 73) corresponded to her medical status age and psychosocial factors No meas*ures were considered indicated*

Of the women in *medical status group II* the household activity of one (No 91) was in accordance with her medical status and age In one patient (No 26) walking up steps was pronouncedly decreased and she had to pass *4 flights of stairs to reach the en*trance of her flat It was old fashioned and had no running warm water no electric stove no rubbish chute which would facilitate the care of the house *although the patient* would nevertheless probably never be able to manage her household *alone If she* could move

to a flat on the ground floor she would be able to go out

Of the other women in group II three (Nos 42 65 72) were judged as able to become fully active in the household and two (Nos 26 79) could probably do more work in the household but not become entirely independent

One patient (No 65) was a 57 year old woman who lived in the country together with her children and husband who was out at work. She had full function of the right arm moderately decreased function of the right leg and decreased cerebral function. Her motivation was decreased and she was overprotected by her husband. Her husband had heavy work as a farm labourer. The home was very poor and it had no running cold water no indoor toilet no central heating no electric stove no refrigerator and no rubbish chute. Attempts should be made to improve the patient's motivation the patient should be trained to do full housework and the husband should be informed of the importance of stimulating the patient to work. The home should be equipped with modern conveniences which would markedly facilitate the care of the house

One patient (No 6) in *medical status group III* was a 56 year old widower who was living together with his 18 year son who was out at work. Function of the right arm was pronouncedly decreased that of the right leg slightly. He had full cerebral function and moderate expressive dysphasia. The house had no indoor toilet no central heating running hot water refrigerator or rubbish chute. A woman, paid by the community prepared the patient's food and cleaned the house. It was thought that the patient could learn to do this work himself but it would require training at a rehabilitation centre. A home with all modern conveniences would considerably decrease his degree of dependence

Patient No 53 was judged as being able to do more household work but probably not become fully active. His home was very simple and had no modern conveniences

Patients Nos 27 and 74 in group III helped their wives with the housework. There was no reason to try to increase the household activity of these two patients

Of the female patients in medical status group III the household activity of three (Nos 13 52 71) corresponded to their medical status

Patient No 30 in group III was a 74 year old woman living together with her husband who was out at work. The function of her right arm and leg was pronouncedly decreased and she had slight dysphasia. Her motivation was strikingly good. Her home had no indoor toilet no running warm water and no rubbish chute. The patient's activity in the household could probably be increased by training at a rehabilitation centre and after improvement of the home and equipment of the kitchen with technical aids for one armed persons. But she could presumably never become fully active

Of the remaining 3 patients in medical status group III two (Nos 48 and 85) were judged as being able to be

come fully active in the household and the third (No 73) as being able to increase her household activity

Patient No 48 was a 60 year old housewife living together with her husband, who was out at work. The function of the left arm was pronouncedly decreased, that of the left leg was moderately decreased, cerebral function was decreased and motivation was pronouncedly decreased. The patient was overprotected by her husband who did most of the housework besides his occupation. Her home was well equipped except that the kitchen had a gas-stove and not an electric stove. Steps had to be passed to enter and leave the house. The patient required treatment at a rehabilitation centre so that she could train walking on level ground by herself and learn to walk up steps and be fully active in the household. The kitchen should be equipped with an electric stove and technical aids for one armed persons. The husband should also be advised to adopt a less protective attitude

The household activity of 2 women in *medical status group IV* could not be increased because pronouncedly decreased cerebral function made them inaccessible to rehabilitation

Inactivity in household

Of the men in *medical status group II*, one (No 67) was occupationally active. He was 28 years old and lived together with his wife. Cerebral function was decreased as was motivation, and he could hardly be expected to do any work in the household in addition to his occupation

Patient No 81 was a 60 year old man living together with his wife who was occupationally active. Cerebral function and motivation were decreased. He had never done any housework before and he was not at all interested in such work. It was not thought that he could be encouraged to do housework

The third patient (No 70) in group II was a hairdresser with a disability pension and living together with his wife. The function of the right arm was slightly decreased but he had full function of the right leg, full cerebral function and moderate, expressive dysphasia. His motivation was good, but his wife was overprotective because of her anxiety about his disease. She had a business of her own and did all her housework herself. Attempts should be made to stimulate the patient to be active in the household, first to provide him with some occupation and secondly, to help his wife

Of the 8 men in *medical status group III* the household activity of 6 (Nos 4, 25, 32, 49, 85, 87) corresponded to their medical status, age and psychosocial factors. The household was looked after by a female relative who was not out at work. There was no reason to try to increase the household activity of these 6 men

Two patients (Nos 17, 61) could probably become partly or fully active in the household

Patient No 17 was a 52 year old married man with pronouncedly decreased function of the left arm, mod

rately decreased function of the left leg decreased cerebral function and mitral stenosis without signs of incompensation He was living together with his wife who in summer looked after a kiosk which she managed besides her own household Her anxiety for the patient made her overprotective The patient could probably learn to be more active in the household for which he should preferably be trained at a rehabilitation centre Attempts should also be made to make his wife less protective

The household activity of 2 women (Nos 57 76) in group III both living with married children corresponded to their medical status One of them (No 57) could probably not become active in the household The other (No 76) was a 66 year old woman with pronouncedly decreased function of her left arm and moderately decreased function of the left leg besides which she had cardiosclerosis without signs of incompensation She also had mental depression which required treatment If such treatment proved successful the patient should receive training at a rehabilitation centre in order to learn how to do most or possibly all of the housework

All 8 patients in *medical status group IV* were judged as not accessible to rehabilitation as far as housework is concerned The female patient (No 3) was 53 years old and function of the left arm and leg was pronouncedly decreased cerebral function was pronouncedly decreased and she had moderately decreased bladder control She was looked after entirely by her husband who also did all the house work

Comments Of those who were partly active in the household one third (2 men and 5 women) could probably become fully active and one fifth (1 man and 4 women) could probably increase their activity but not become fully active Of the 21 inactive patients one fifth (3 men and 1 woman) were judged as being accessible to rehabilitation Of these one man could probably become fully active and the remaining patients partly active in the household with a certain reservation for one (No 76) of the latter

Most of the men and women who were fully active had full or only slightly decreased function of the arm and/or leg and full cerebral function

Those who were partly active in the household or inactive and judged as being accessible to rehabilitation had some of the following characteristics Full to pronouncedly decreased function of the arm Full to moderately decreased function of the leg Full to decreased cerebral function Full to pronouncedly decreased motivation Some of the patients were overprotected

Rehabilitation should include *inter alia* the following measures Most of the patients required physio therapy Admission to a rehabilitation centre was considered indicated in 5 patients who required training at a rehabilitation kitchen Attempts to improve motivation were indicated in 7 cases and in 5 the patient s relatives should be advised to be less protective The

homes should be improved in 7 cases

Two patients Nos 36 and 6, were equal from a medical point of view One was fully active in the household, the other, only partly Their homes differed widely That of the former was satisfactory, while that of the latter was very poor It is probable that the poor state of the home contributed to the decreased household activity of the latter

As expected, men were more often inactive in the household than women of corresponding medical status This can probably be explained to some extent by the relatively high age of most of the patients in this series and by the conventional distribution of the work between men and women in that generation The men had often only learned how to manage their occupation they had never learned to do anything in the house and when pensioned off they were inactive in the household Most of these women had been fully occupied with their household for several years In the event of a chronic disease such as hemiplegia they are therefore probably better able to perform those duties which they have been used to than are men who must learn and adopt a new attitude to housework It is however of interest to note that the women often did a considerable amount of work in their home despite their decreased medical status For the men who were not occupationally active however light housework provides a possibility of doing something and of giving them a feeling that they are making themselves useful despite their disease In such cases where the man is looking after the house, his activity in the household must be regarded as productive work An intermediate position is occupied by pensioners active in the household and living together with vocationally occupied wives

As pointed out in the section on self care the use of a wheel chair in selected cases would be useful But this would require appropriate modification of the kitchen if the patient is to increase his activity in the household

Vocational activity

Vocational activity as the goal of rehabilitation is important for all patients especially for those with dependants and for the economy of the country

Table 58 shows that those who were fully or partly vocationally occupied belonged to medical status groups I II and III and that none belonged to group IV However some patients in all three medical status groups were inactive One might expect that those who are inactive and belong to groups I and II and possibly some of those in group III are accessible to vocational rehabilitation On the other hand the medical status of the patients in group IV would not allow them to become vocationally active

Full vocational activity

The vocational activity of the 4 patients (Nos 8 9 22 28) in *medical status group I* who were fully active corresponded to their medical status

Table 38 Vocational activity and medical status groups

Groups[1]	Vocational activity						Total
	F		D		N		
	♂	♀	♂	♀	♂	♀	
I	2	2	—	1	1	3	9
II	1	—	—	1	2	3	7
III	1	—	1	—	9	10	21
IV	—	—	—	—	7	3	10
Total	4	2	1	2	19	19	47
	6		3		38		

[1] Key to symbols and abbreviations is given on page 20

Case No 67 in *medical status group II* was a 28 year old married man with full function of the left arm slightly decreased function of the left leg decreased cerebral function and motivation He was a lorry driver and had undergone vocational training as a welder He found it difficult to adjust himself to his new occupation and should therefore be motivated further

Patient No 74 in *medical status group III* was a 65 year old farmer whose only sequelae after hemiplegia was slightly expressive dysphasia He had however cardiosclerosis without signs of incompensation but with roentgenologically demonstrated general enlargement of the heart and auricular fibrillation without deficit The patient was too active and should preferably do lighter work He could achieve this by placing more work upon his assistant

Decreased vocational activity

The decreased activity of 2 women (Nos 86 78) in *medical status groups I and II* corresponded to their medical status and psychosocial factors

Patient No 85 in *medical status group III* was a 55 year old man with pronouncedly decreased function of the right arm moderately decreased function of the right leg slightly decreased ability to travel Motivation was strikingly good Together with his sister he managed a market garden Since he was working for his own account he could decide the rate at which he worked His performance was good for his medical status probably because of his good motivation

Vocational inactivity

Patient No 14 in *medical status group I* was a 60 year old widower living alone

He had recovered almost completely from his right sided hemiplegia He had been an engineer on a cargo boat and was now receiving a disability pension *In view of his medical status* attempts should be made to find him a shielded occupation

Patient No 39 was a 45 year old married housewife She had recovered completely from her hemiplegia and had full cerebral function Her only *child was grown up* She herself thought she had too little to do in the household and said spontaneously that she would like to take up some occupation

The other two women *(Nos 37, 51)* in medical status group I were fully *active in the household, which means* that they had continued with the work they had before the onset of the disease Vocational rehabilitation was not considered indicated in these cases

As to two men (Nos 50, 81) in *medical status group II,* attempts should perhaps *be made to find them a shielded* occupation, despite their ages, 65 and 64 years

The 3 women in medical status group II were active in the household All had been occupied in the household before their disease Vocational *training* for these women was not considered indicated

Of the 9 men in medical status group III it was thought that vocational training was indicated for one *(No 15)* and that six (Nos 4, 6 17 36 53 61) should be given shielded occupation In 2 cases (Nos 32, 80) vocational training was not considered indicated

Patient No 15 was a 24 year old unmarried man who was living with his parents He had recovered completely from his left *sided hemiplegia but he* had a congenital valvular heart disease (stenosis valvulae pulmonalis? + ventricular septum defect?) without signs of incompensation and with roentgenologically demonstrated normal sized heart His motivation was decreased *Vocational training* was indicated This should be done in consultation with a cardiologist

Patient No 36 was a 58 year old former swimming master who was living alone and receiving a disability pension Function of the right arm was pronouncedly decreased, he had full function of the right leg and full cerebral *function, slightly expressive dys*phasia and good motivation He felt lonely It was thought that he could learn to do simple manual work Because of his pronouncedly decreased function of the arm and the dysphasia he should receive vocational training *at a rehabilitation centre*

Patient No 6 was a 56 year old market gardener *with pronouncedly* decreased function of the right arm slightly decreased function of the right leg full cerebral function and moderate expressive dysphasia It was thought that he could manage a shielded occupation but because of his *decreased function* of the arm and dysphasia he should first receive train*ing at a rehabilitation centre*

Patient No 4 was a 65 year old man who had completely *recovered from his* left sided hemiplegia He had slightly decreased cerebral function and cardiosclerosis without signs of incom

pensation Attempts should perhaps be made to find a shielded occupation for him despite his age

Of the 10 women in medical status group III 7 (Nos 13 48 52 55 66 88 90) were fully or partly and three (Nos 20 41 76) were inactive in the household In no instance was vocational training considered indicated These 7 patients active in the household had been active in the household also before their disease

No patient in *medical status group II* was considered accessible to vocational training

Comments None of the partly active patients were considered capable of increasing their occupational activity

As to those who were inactive (38) some form of vocational rehabilitation appeared possible for one fourth (11 10 men and 1 woman) Of these it was thought that 2 could return to work in the open market and that the others (9) could manage a shielded occupation As to 3 of the last mentioned group however age was a relative hinder

Shielded work is admittedly less profitable but it offers the patient an opportunity to do something useful and prepare for work in the open market

The vocationally inactive men who were judged as accessible to vocational rehabilitation had *inter alia* the following characteristics Full slightly or pronouncedly decreased function of the arm full or slightly decreased function of the leg Full or decreased cerebral function Little or no expressive dysphasia Full or slightly decreased ability to travel Full or slightly decreased motivation Apart from three cases the patients were at most 60 years of age

Most of the men belonging to medical status groups I II and III were judged as being accessible to some form of vocational rehabilitation but only one woman

The only woman for whom vocational training was considered indicated was relatively young She had recovered completely from her hemiplegia and she felt that her housework was not enough for her Compared with this woman the other occupationally active women were as a rule older and/or in a poorer medical status group and/or dependent upon other psychosocial factors Some of these women had however again become fully active in the household There was no indication to motivate these women to take up any vocation

CHAPTER VI

General discussion

It appears that systematic, intense research in the field of rehabilitation is desirable (Samordnad rehabilitering, S O U 50—51 1964) It has been stressed that rehabilitation should not be confined to those who can return to work but should be extended to include the aged and patients with chronic diseases who cannot be expected ever to work again This extension is justified not only because of its humanitarian value and the scarcity of nursing personnel, but also because improvement in the patient s performance means a decrease in the burden of nurses and assistants and thereby also a decrease of expenditure

A fundamental link in a rehabilitation programme is the availability of methods with which we can measure *the degree of disability of a given patient* and secondly various features of his environments so that we can decide whether he is *accessible to rehabilitation* and if so what measures should be taken

The need of more refined methods for measuring disability according to suitable scales has been empasized by Peszczynski (1960) and Litman (1964)

With this in mind a method was devised which is based on the interplay or mutual effect of medical status psychosocial factors and sociomedical performance and which allows evaluation of the patient s situation and indications for rehabilitation

Knowledge of the extent to which the *sociomedical performance in a given* case depends on psychosocial factors is necessary if rehabilitation is to be causal Systematic description of all of the above factors in each case will reveal any defects All such defects must be attended to and corrected if they suppress the patient s performance Rehabilitation concentrated only on the patient and not taking such psychosocial factors into account must be inadequate

If a method for assessing the indications for rehabilitation is to be satisfactory the variables studied must be properly selected and well defined and suitable scales must be devised This *part of the method* was *based* partly on literature studies and partly on clinical experience

Grading of different *levels* of the subvariables according to their importance for the patient s disability provides a functional operational definition of the respective levels of the subvariable This basis for grading the

subvariables implies a possibility to utilise numerical and more precise expressions than conventional verbal descriptions such as "slight", "moderate" etc. The numerical differences between different levels enables the reader once he has become versed in the system to form an opinion at a glance of the situation of a given patient. The large differences also remind the reader that the number of points are not arithmetic values.

All the subvariables of the main variable medical status are taken together in the form of a single point constellation of values. This gives ready approximate information of the patient's medical status. Division of medical status into 4 groups allows a rapid opinion of the severity of a patient's degree of disability.

Of the main variables sociomedical performance and psychosocial factors only the subvariables of self care and of home conveniences lent themselves to be taken together to a point constellation. This was because other subvariables were either too different in their nature or because they overlapped one another. In the latter case a common point constellation would might mean an exaggeration of the patient's disability.

Certain subvariables can be better expressed verbally than by a scale. The term "no occupational activity" is readily understood, besides which it would be misleading to give a woman 1000 points just because she has no occupational activity though she looks after the household for a large family.

The intention of such a high value as 1000 points for the medical subvariables was to reserve the limited expensive resources necessary for advanced rehabilitation for cases in which such treatment is really worthwhile. This point level value is thus of decisive importance and should be used with caution. This is all the more important when the method is applied to patients who have just passed the acute stage and in whom, in contrast to the chronic group studied, the medical and the sociomedical subvariables can be expected to change considerably either spontaneously or with the aid of rehabilitation in the narrow sense of the term. Repeated examination at intervals of *e.g.* 1, 2 and 3 months in such cases may facilitate the *decision*.

Only a few levels were used for each variable. It is true that this decreases the possibility of a very precise differentiation in a given case, but increases the reliability of the method.

For some subvariables it was necessary to use simple examination methods and to limit the number of subvariables of all of the *main* variables in order not to make the method unwieldy. The method can therefore also be applied without difficulty by any physician in charge of patients with hemiplegia.

Physicians working at rehabilitation centres may feel that the methods does not cover sufficient details on *e.g.* self care and other activities of daily living. Detailed descriptions of such performances are available (Sokolow *et al.* 1958, Rusk 1964, Kottke 1965, Dinnerstein 1965).

Certain covariations were found be

tween the subvariables of each main variable This was demonstrated partly by *frequency distributions* and partly by the levels of the patients in certain varying cross tables In the same way together with the case reports it was found possible to show the degree dependence of sociomedical performance on medical status and psychosocial factors

The accessibility of each case to rehabilitation was judged according to the goal of such rehabilitation, *i e* self-care, household and vocational activity The evaluation of the possibility of the patients to achieve these goals was realistic and was based on a system of items included in medical status, *psychosocial factors and socio* medical performance In doubtful cases the goal of rehabilitation will of course vary somewhat with the clinical experience of the examiner A verification of the patients possibility to achieve the goals set in accordance with the present method requires the availability of adequate rehabilitation services which *are lacking in most dis* tricts in Sweden

It should be pointed out that the re sults of rehabilitation can be influenced by a variety of factors *e g*, recurrence supervention of a serious disease, deterioration because of rapid aging and sudden death

The above mentioned goals of rehabilitation are the main goals which can be modified according to circumstances It should be emphasized that *the goals set should be such as can* presumably be achieved (Lamb et al *1963*) firstly in the interest of the patient and, secondly, not to throw an unnecessary burden on rehabilitation centres

The measures suggested are those which were *found most urgent in the* application of the present method *These measures can of course be modi* fied during treatment

Judging from the results obtained the method appeared informative The subvariables selected thus appear to be relevant in the evaluation of the accessibility of a patient to rehabilitation Classification within each sub variable by a number of points or sym *bols proved useful in that it describes* the position of the patient in each variable in a meaningful way *i e* his disability

Though the results obtained in the present investigation concerning accessibility to rehabilitation are not representative of all hemiplegics in Malmö hus län or in Sweden they do illustrate the importance of the problem A large number of hemiplegics in Sweden are *thus in urgent need of* rehabilitation for which no resources are yet available

It is suggested that the method should be applied to a *large and repre* sentative material The results of such an investigation could be used in the calculation of the rehabilitation services necessary in the country

Summary

A method for evaluating the accessibility of patients with chronic hemiplegia to rehabilitation is described The method is based on three main variables medical status socio-medical performance and psychosocial factors Each main variable is based on certain subvariables selected to describe the degree of disability from a functional point of view These subvariables have different levels which together form an ordinal scale A precise definition is given of each step of such a scale and is described by a number of points or by a graphical or verbal symbol When described by points each of the steps was allotted 0 1 10 100 and 1000 points These numbers denote intervals and are not to be regarded as arithmetic values In this investigation only 2—4 levels were used for each variable The gradation of the scale varies with the disabling effect of the variable The level 0 point indicates the absence of physical handicaps of decreased performance or of disturbing psychosocial factors

The subvariables of the main variable medical status are function of arm respectively leg cerebral function speech vision hearing bladder and bowel control and co existing diseases Of the subvariables of medical status those that can dominate the patient s disability have been given 1000 points for their maximum level which also means that the patient is practically inaccessible to rehabilitation

The subvariables of the main variable sociomedical performance are ability to eat to dress and to manage personal hygiene to walk on level ground and up steps to travel as well as household activity and vocational activity

The subvariables of the main variable psychosocial factors are motivation overprotective attitude of relative, form of abode family constellation home help type of house size of home conveniences (toilet hot and cold water etc) telephone unavoidable steps at entrance of house distance to nearest grocer s shop to neighbour and the patient s economic situation

If the numbers allotted to a given patient for the various subvariables of medical status be written one after the other it will give a point constellation reflecting the medical status of the patient

According to the appearance of the point constellation the series was divided into 4 medical status groups I

II, III and IV, of increasing disability Group I comprises patients with little or no impairment of medical status, full sociomedical performance may be expected of these patients Group IV comprises patients with pronouncedly impaired medical status and in these the sociomedical performance can be expected to be pronouncedly decreased Patients in this group are practically inaccessible to rehabilitation Groups II and III consist of patients with slightly to moderately impaired medical status and their performance can be expected to be unimpaired or slightly to moderately decreased Some of the patients in this group are probably accessible to rehabilitation

As for the main variables sociomedical performance and psychosocial factors, only the subvariables belonging to self care and conveniences in the home were expressed by a point constellation, after which the patients were grouped

By comparing subvariables of one and the same main variable, it can be shown whether any subvariable varies in relation to another

Systematic comparison between sub variables or groups of subvariables belonging to the main variables medical status sociomedical performance and psychosocial factors, reveal the pa patient's disability and accessibility to rehabilitation and suggest what measures may be indicated

In the evaluation of accessibility to rehabilitation the goal set should be such as can be expected to be achieved by the patient provided adequate measures are taken

The primary material consisted of 377 consecutive admissions for an initial attack of hemiplegia These patients were seen at the Medical clinic, Lasarettet, Lund during a 10 year period 1949—1958 The surviving 91 patients were examined in their homes in 1960

The method described was tried on these 91 patients

Certain covariations were found between subvariables of the same main variable as well as between subvariables or groups of subvariables of different main variables

The accessibility of the patients to rehabilitation was judged with the following goals in mind self care, household activity and vocational activity

The rehabilitation programmes suggested covered a wide variety of measures including advanced forms of treatment at open or closed institutions measures enabling the patient to return to some occupation and environmental changes

Judging from the results obtained the method was well adapted to its purpose It is suggested that it should be applied to a large representative material The results of such an investigation would provide a fundamental link in the planning of the necessary rehabilitation services which are still lacking in most districts of Sweden

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As for the main variables sociomedical performance and psychosocial factors, only the subvariables belonging to self care and conveniences in the home were expressed by a point constellation, after which the patients were grouped.

By comparing subvariables of one and the same main variable, it can be shown whether any subvariable varies in relation to another.

Systematic comparison between subvariables or groups of subvariables belonging to the main variables medical status, sociomedical performance and psychosocial factors reveal the patient's disability and accessibility to rehabilitation and suggest what measures may be indicated.

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41	I	C?		B	H	71	r	1	κ	10	01				0	1 0
1	M		6	M	B	118	l	101	10	1			σ			
10	I	C2	)	M	H	83	l		1		0	0		)	0	
47	M	46	7	M	M	1 1	r	10	0	100 1	1		)	1	)	
48	I	1	60	M	H	110	l	100	[illegible]	10		0	0	)	0	0
49	M	63	C7	M	B	11	l	100	100	10	(	)	0	10	0	0
0	M	6	C	S	M	110	l	1	1	0	0	0	0	)	[illegible]	[illegible]
1	I	44	1	M	H	0	l	0	0	0	0	0	)	0	0	0
	I	1	[illegible]	M	H	1	l	10	10	1 1	0	0	0	)	0	0
3	M	7	[illegible]	S	M	14	l	0	0	0	0	)	0	0	0	0
1	I	61	0	M	B	C	l	0	10	0	0	0	0	)	0	0
[illegible]	I	6	6	M	H	39	r	0	0	0	0	0	0	0	0	0
6	I	C7	C9	W	M	1	r	1 0	[illegible]	1000	0	0	0	0	10	0
7	I		81	W	H	9	l	100	10	0	0	0	0	100	1	0
u4	M		77	W	B	46	r	[illegible]	[illegible]	1000	0	0	0	0	1	10
0	M	3	6	M	S	1 1	l	100	100	1000	0	0	0	0	0	[illegible]
C0	M	60	67	S	M	?7	l	100	100	1000	0	0	0	)	0	0
61	M	45	3	S	B	9	l	0	100	10	0	0	0	0	0	0
C	F	o4	8	W	M	48	l	1	0	0	0	0	0	0	0	0
63	I		4	W	H	63	r	100	100	0	1	0	0	0	0	0
61	I	0	77	S	D	7o	l	110	100	1000	0	0	0	0	100	0
0	I	5	7	M	H	63	r	0	[illegible]	10	0	0	0	0	0	0
)	I	)	0	W	M	9	l	0	10	0	0	0	0	0	0	0
67	M	?4	8	M	M	14	l	0	1	10	0	0	0	0	0	0
C8	M	o	61	M	S	117	r	100	10	1000	1	0	0	0	10	10
	M	41	?	S	M	119	l	100	10	1010	0	)	0	0	0	0
0	M	C0	C7	M	S	7	r	1	0	0	10	0	0	1	1	0
71	I	C	71	M	H	61	l	100	10	10	0	0	0	0	0	0
7	I	61	1	S	S	87	r	0	0	10	0	0	0	0	1	0
3	I	64	71	M	H	83	r	1	10	10	0	0	0	0	10	0
74	M	61	C	M	M	41	r	0	0	0	1	0	0	0	0	0
7	I	C8	71	M	B	63	r	0	0	0	0	0	0	0	0	0
6	I	61	C0	W	H	47	l	100	10	10	0	0	0	0	1	0
77	I	C0	74	W	H	(	l	100	100	1000	0	0	0	1	1	0
8	I		4	W	S	37	r	1	0	)	0	0	0	0	0	0
)	I	C0	7	M	M	13o	l	10	1	10	0	0	0	10	1	0
80	M	6	[illegible]	S	M	7?	r	0	100	10	1	1	0	1	1	0
81	M	60	64	M	S	47	l	0	0	[illegible]	0	0	0	0	0	0
4	I	6o	76	W	H	111	r	100	100	1000	100	0	0	0	1	100
83	I	C6	1	M	H	61	l	0	0	10	0	0	0	0	0	0
84	I	C9	0	W	H	118	r	[illegible]	0	0	0	)	0	100	0	0
8	M			S	S	31	r	100	[illegible]	0	1	0	0	0	0	0
86	F	11		W	H	1 7	l	1	0	0	0	0	0	0	0	0
87	M	6	64	M	S	38	l	1	1	10	0	0	0	0	0	0
88	I	3	41	M	H	100	r	100	[illegible]	10	10	0	)	0	0	0
89	I	)	81	W	H	1?	l	100	100	1000	0	0	0	0	100	100
0	I	C3	C5	M	H	18	l	)	0	1)	0	0	0	0	0	0
1	I	5	83	W	H	10	r	)	[illegible]	0	0	0	0	0	0	0

J f H S ig] H l crea 1 M lerat ly leerea 1 1 jr no nee H l ereas 1 f H n D leere l fun H n
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I = f H D l crea 1 1 j r ce lly 1 er a 1 1 val o t

Table 39 Survey of cases

Int No	Sex	Age in years at: onset	Age in years at: after exam	Civ stat M = married, S = single, W = widow(er), D = divorced	Vocation B Brain worker, M — Manual worker, H House wife, V = Various	Interval between onset and after exam (months)	Side of hemiplegia l left, r right	Medical status: Arm[1] 0 = I, 1 = S, 10 = M, 100 = P	Leg[1] 0 = I, 1 = S, 10 = M, 100 = P	Cerebral[1] 0 I, 10 D, 1000 = P	Speech (dysphasia)[2]: Expr 0 = N, 1 = S, 10 = M, 100 = P	Impr 0 N, 1 S, 100 M, 100 P	Glob 0 N, 100 P	Vision[1] 0 = I, 1 S, 10 = M, 100 = P	Hearing[1] 0 I, 1 = S, 10 M, 100 = P	Bladder[1] 0 = I, 10 = D, 100 = I
1	F	69	73	W	H	45	r	100	100	1000	100	0	0	0	1	100
2	M	53	63	S	M	117	r	100	0	1000	0	0	0	0	0	0
3	F	51	53	M	H	32	l	100	100	1000	0	0	0	0	0	10
4	M	62	65	M	M	36	l	0	0	10	0	0	0	0	0	0
5	M	71	73	M	M	33	r	100	10	1000	0	0	0	0	0	0
6	M	45	56	W	M	130	r	100	1	0	10	0	0	0	0	0
7	F	54	60	S	H	70	l	100	100	1000	0	0	0	1	100	100
8	F	28	38	D	H	119	r	0	1	0	0	0	0	0	0	0
9	F	49	55	D	B	67	r	0	0	0	0	0	0	0	0	0
10	F	57	62	S	M	19	l	10	10	1000	0	0	0	0	0	0
11	M	58	60	M	B	47	l	100	100	1000	0	0	0	0	0	0
12	M	69	74	W	B	59	l	100	100	1000	0	0	0	1	0	0
13	F	52	58	M	H	71	r	0	0	10	1	1	0	0	10	0
14	M	58	60	W	M	18	r	0	0	0	0	0	0	0	0	0
15	M	18	23	S		85	l	0	0	0	0	0	0	0	0	0
16	F	69	78	M	B	116	l	0	0	0	0	0	0	0	0	0
17	M	42	52	M	V	125	l	100	10	10	0	0	0	0	0	0
18	M	75	78	W	M	51	l	100	1	0	0	0	0	0	1	0
19	F	72	74	W	H	17	l	1	0	10	0	0	0	0	100	0
20	F	68	70	W	H	52	l	0	0	0	0	0	0	0	0	0
21	F	33	43	M	H	117	l	1	1	10	0	0	0	0	0	0
22	M	32	43	M	M	129	l	0	0	0	0	0	0	0	1	0
23	F	68	72	W	H	73	r	0	0	1000	0	0	0	1	0	0
24	M	67	75	M	M	91	r	0	0	0	0	0	0	0	0	0
25	M	71	75	M	M	30	l	0	0	0	0	0	0	0	1	0
26	F	67	70	W	V	104	r	10	[illegible]	0	0	0	0	0	0	0
27	M	66	73	M	M	80	r	0	0	0	0	0	100	0	0	0
28	M	44	79	M	M	61	r	0	0	0	0	0	0	0	0	0
29	F	59	61	M	H	60	r	100	100	0	1	0	0	0	0	0
30	F	71	71	M	H	29	r	100	100	0	1	0	0	0	1	0
31	F	61	71	M	H	83	r	0	0	1000	0	0	0	1	1	0
32	M	47	65	M	V	85	l	100	[illegible]	0	0	0	0	0	0	0
33	F	70	71	S	V	16	l	0	0	1000	0	0	0	0	0	0
34	F	61	75	S	M	130	l	0	0	0	0	0	0	0	0	0
35	M	61	65	W	M	71	r	100	1	0	10	0	0	1	0	10
36	M	47	49	D	M	125	r	100	0	0	1	0	0	0	[illegible]	0
37	F	54	61	M	B	85	r	0	1	0	0	0	0	0	0	0
38	M	71	73	M	M	91	l	100	100	1000	0	0	0	0	0	0
39	F	42	45	M	H	11	r	0	0	0	0	0	0	0	0	0
40	F	62	68	W	V	70	l	0	0	10	0	0	0	0	1	0
41	F	44	50	D	M	68	r	100	10	10	1	0	0	0	0	0
42	F	66	71	M	H	52	r	0	0	10	[illegible]	0	0	1	0	0
43	F	70	79	W	H	16										

	0	0	11	II	0	0	0	0	F	0	0	0	I	
	0	100	22	III	0	100	10	110	M	[illegible]	1000	1000		N
	0	1	1[illegible]	II	0	0	0	0	I	0	0	0	D	
	0	0	10	II	0	0	0	0	I	0	0	0	I	
	30	100	[illegible]00	IV	10	1000	1000	[illegible]010	I	1000	1000	1000		
	0	100	1300	IV	10	100	100	210	M	1000	1000	1000	N	N
	0	1	1	I	0	0	0	0	I	0	0	0	I	
	0	1	10[illegible]2	IV	[illegible]	[illegible]	[illegible]	[illegible]	S	10	10	100	N	N
	0	1	121	III	10	100	10	120	M	1	1000	1000	D	N
	0	100	3[illegible]0	III	100	1000	1000	2100	P	1000	1000	1000	N	
	0	1	3	II	0	0	0	0	I	1	1	1	I	N
	0	1	1	I	0	0	0	0	I	0	0	0	I	N
	0	100	130	III	10	100	10	120	M	10	10	1000	D	N
	0	100	100	III	0	0	0	0	I	0	0	0	D	N
	0	1	11	II	0	0	0	0	I	[illegible]	10	100	I	
	0	100	100	III	0	0	0	0	I	0	0	0	I	N
	0	0	1120	IV	10	100	100	210	M	10	1000	1000		
	0	1	212	III	10	10	100	120	M	10	10	1000	N	
	0	100	1131	IV	10	1000	1000	2010	P	1	1	1000		
	0	1	1201	IV	100	1000	100	1200	P	1000	1000	1000	N	N
	0	0	1200	IV	10	1000	1000	2010	L	1000	1000	1000		
	0	100	210	III	0	100	100	200	M	1000	1000	1000	N	N
	0	1	2	II	0	0	0	0	I	0	0	0	I	N
	0	100	301	III	10	1000	1000	2010	P	1000	1000	1000		
	0	100	1100	IV	10	1000	100	1110	P	1000	1000	1000		
	0	1	21	II	0	0	0	0	I	10	10	1000	D	N
	0	0	10	II	0	0	0	0	I	10	10	1	I	N
67	0	0	11	II	0	0	0	0	I	0	0	0	N	I
68	0	1	1132	IV	0	0	0	0	I	1	1	1	N	N
69	0	0	1110	IV	10	0	10	20	S	10	1000	1000		N
70	0	1	13	II	0	0	0	0	I	1	1	100	N	
71	0	100	220	III	10	10	0	20	S	1	1000	100	D	
72	0	0	11	II	0	0	0	0	I	0	0	0	D	
73	0	100	111	III	0	0	0	0	I	1	10	1000	D	
74	0	100	101	III	0	0	0	0	I	0	0	0	D	I
75	0	1	1	I	0	0	0	0	I	0	0	0	D	
76	0	100	221	III	0	[illegible]	1000	1010	L	10	[illegible]	1000	N	N
77	0	100	130[illegible]	IV	10	1000	100	1110	P	1000	1000	1000		
78	0	1	2	II	0	0	0	0	I	0	0	0	I	D
79	0	1	33	II	0	10	10	20	S	0	0	100	D	
80	0	100	213	III	0	100	10	110	M	10	1000	1000		N
81	0	1	11	II	0	0	0	0	I	0	0	0	N	N
82	1000	1000	1301	IV	1000	100	1000	2100	P	1000	1000	1000		
83	0	0	10	II	0	0	0	0	I	0	0	0	I	
84	0	100	210	III	0	0	0	0	I	0	0	1000	I	
85	0	0	111	III	10	0	0	10	S	1	10	1	N	D
86	0	0	1	I	0	0	0	0	I	0	0	0	I	D
87	0	100	112	III	10	[illegible]	10	30	S	1	1	100	N	
88	0	0	130	III	10	100	10	120	M	1	1000	1000	D	N
89	1000	1	2301	IV	1000	1000	1000	3000	P	1000	1000	1000		
90	0	0	[illegible]	II	0	0	0	0	I	0	0	1	I	N
91	0	1	11	II	0	0	10	10	S	10	1000	1000	D	

Table [illegible] (Continued)

Pat No	Medical status				Sociomedical performance[3] (See note page 101)									
	Bowel[3]	Co-existing disease or symptoms	Score	Med stat groups according to score	Self-care					Walking ability		Ability to travel	House work at home	Vocational activity < 67 yr
					Eating	Dressing	Hygiene	Score	Performance according to score	Level ground	Steps			
	0 = I 100 = II 1000 = I	0 = None 1 = Not disabling 100 = Disabling 1000 = Contra indic. rehab		Min max I 0 1 II 2 71 III = 100 810 IV = 1000 3600	0 I 10 = S 100 M 1000 P	0 I 10 = S 100 = M 1000 = P	0 = I 10 = S 100 = M 1000 = P		Min Max I = 0 0 S = 10 30 M = 100 300 P = 1000 3000	0 I 1 = S 10 = M 1000 = P	0 = I 1 = S 10 = M 1000 = P	0 = I 1 = S 100 = M 1000 = I	I D N	I D N
1	100	1	1501	IV	1000	1000	1000	3000	P	1000	1000	1000		
2	0	100	1200	IV	0	0	0	0	I	0	0	1000		N
3	0	0	1210	IV	10	1000	1000	2010	P	1000	1000	1000	N	N
4	0	100	110	III	0	0	0	0	F	0	0	0	N	N
5	0	1	1111	IV	10	100	10	120	M	10	10	1000	N	
6	0	0	111	III	10	0	0	10	S	1	1	100	D	N
7	1000	1	2102	IV	1000	1000	1000	3000	P	1000	1000	1000		N
8	0	0	1	I	0	0	0	0	F	0	0	0	F	I
9	0	1	1	I	0	0	0	0	F	0	0	0	F	F
10	0	1	1021	IV	0	100	100	200	M	10	10	100		N
11	0	100	1300	IV	10	1000	1000	2010	P	1000	1000	1000		N
12	0	1	1202	IV	10	1000	100	1110	P	10	1000	1000	N	
13	0	100	121	III	0	0	0	0	F	0	1	1000	D	N
14	0	1	1	I	0	0	0	0	I	0	0	0	D	N
15	0	100	100	III	0	0	0	0	F	0	0	0	I	N
16	0	0	0	I	0	0	0	0	F	0	0	0	F	
17	0	100	220	III	0	100	100	200	M	10	10	1	N	N
18	0	100	202	III	0	10	10	20	S	1	1	1		
19	0	100	211	III	0	0	0	0	I	0	0	0	F	
20	0	1	1	I	0	0	0	0	F	0	0	0	F	
21	0	0	12	II	0	0	10	10	S	0	0	0	F	N
22	0	0	1	I	0	0	0	0	F	0	0	0	I	F
23	0	0	1001	IV	0	0	0	0	I	0	0	100	D	
24	0	1	1	I	0	0	0	0	I	0	0	0	D	
25	0	100	101	III	0	0	0	0	F	0	0	0	N	
26	0	1	21	II	0	10	10	20	S	10	1000	1000	D	
27	0	1	101	III	0	0	0	0	F	0	0	1000	D	
28	0	0	0	I	0	0	0	0	I	0	0	0	D	I
29	0	0	201	III	10	100	100	210	M	1000	1000	1000		N
30	0	0	202	III	10	100	10	120	M	10	1000	1000	D	
31	0	100	1102	IV	0	0	10	10	S	0	0	100		
32	0	0	110	III	10	100	10	120	M	10	1000	100	N	N
33	0	0	1000	IV	0	0	0	0	I	1	1	1000	D	
34	0	1	1	I	0	0	0	0	I	0	1	0	I	
35	0	0	122	III	10	10	10	30	S	1	1	100		
36	0	0	101	III	0	0	0	0	I	0	[illegible]	0	I	N
37	0	0	1	I	0	0	0	0	I	0	1	0	I	N
38	0	1	1201	IV	10	1000	1000	2010	P	1000	1000	1000	N	
39	0	0	0	I	0									

7			H	1 G		W	11	4	<1
40			H	1	l		3	2	<1
41			I	I		W	I	1k	1—2
4	10		H	1S	l		3	11	2
43	0		H	I			B	1k	1—
41	10		I	1SU	l	D	11	61	<1
4	10	+	H	1S	l	W	II	31	<1
46	0		I	1S	S	D	B	11	
47		+	H	1S	SOR	D	B	1k	<1
48	1	+	H	1S	SC	D	M	4k	1—
41	100		H	1S	CR	M	I	11	<1
0			H	I		—	1C	31	1—
1	0		H	1S	SU	D	II	k	
	100	+	H	1S	OS	D	11	1k	<1
3	10	+	H	1 B	S	D	11	4k	<1
1			H	1S	SC	D	11	3k	
	0		H	1S					
6	10		I		CCR	D	1C	5k	<1
7	0		H	1 CR			B	k	<1
8	1000		I	POR	S	D	1C	5k	<1
9	10		H	1S			1C	I	<1
60	10		I	I			B	11	
61	10	+	H	II	l	D	B	1kC	1—
6	0	—	H	I		—	11	I	<1
63	10		I	1COR			B	9k	1—
64	10		I	1 B			1C	91	1—
6	10	+	H	1SC	S	D	B	9k	<1
66	0	—	H	I	G	W	B	11	
67	11		H	1S		—	B	31	<1
9	10	+	H	1S	S	D			
C	10		I						
0	1	+	H	1S	S	D	B	11	<1
71	1		H	1SC	SL	D	B	4k	
7		+	H	1OR	OR	D	B	I	1—
9	10	+	H	1SC	SC	D	11	31	<1
I			H	1SC		—	1C	k	<1
		+	H	1 C	C	D	11	I	<1
6		+	H	1COI	G	D	11	1	<1
77	1		I	I		W	B	3k	1—
78	0	—	H	I	COR	D	B	11	
I	10	+	H	1S	SU	D	B	11	<1
80	1		I	I			11		<1
81	10	—	H	1S		—	B	31	
8	1		I						
87	0	—	H	1S	SC	D	B	11	<1
81	1	—	H	I	C	W	11	9k	<1
8		—	H	1OR	OR	D	11	9k	<1
80	0	—	H	1C	I	M	1C	k	
87	10	+	H	1S	SOR	D	I	k	1—
88	10	+	H	1SC	SC	M	B	k	1—
89			I						
0	0	—	H	1SC	S	M	B	1	1—
1		—	H	1	I	W	B	11	1—

	Psychosocial factors						Home interior factors		
	Motivation[1] (See note page 101)	Overprotection at home	Abode	Fam constell	Home help: Type	Home help: Frequency	Type of house	Nr of rooms excl kitchen	Persons per room
	0 1 10 = D 1000 = P	+ = Yes — = No ± = Uncertain	H = Home I = Inst	P = Patient S = Spouse C = Child(ren) OR = Other relative U = Unrelated person	Symbols as in preceding column	— = No help M = 1–2 times mth W = 1–3 times wk D = Daily	H = One fam house 2H = Two fam house B = Block of flats	K = kitchen KT = kitchenette KC = kitchen cupboard	<1 1–2 2 >2
1			I						
2	1000		I	P			H	3K	<1
3	10	+	H	PS	S	D	H	4K	<1
4	10	—	H	PSOR		—	B	2K	>2
5	10	+	H	PS	S	D	H	5K	<1
6	0	—	H	PC	U	D	H	2K	1–2
7			I	POR			H	4K	<1
8	0	—	H	PC		—	B	3K	<1
9	0	—	H	P		—	2H	3K	<1
10	10		I	P			H	2K	<1
11	10		I	PSC			B	2K	1–2
12	1000	+	H	PU	U	D	H	5K	<1
13	0		H	PS	SC	D	H	3K	<1
14	0		H	P	C	W	H	3K	<1
15	10	—	H	POR		—	H	3K	1–2
16	0	—	H	PS		—	2H	2K	1–2
17	0	+	H	PS	S	D	H	3K	<1
18	0		I						
19	10	—	H	P		—	B	2K	<1
20	0	—	H	P	C	M	B	1K	1–2
21	0	—	H	PSC	U	M	B	3K	1–2
22	0	—	H	PSC		—	H	4K	<1
23	10	—	H	PC	C	D	H	2K	1–2
24	0	—	H	PS		—	2H	3K	<1
25	0	±	H	PS	OR	M	H	1K	<1
26	0	—	H	PU	U	D	B	1K	<1
27	0	—	H	PS	U	M	H	5K	<1
28	0	—	H	PSC		—	B	3K	1–2
29	0		I	PS			B	1KT	<1
30	0		H	PS			H	1K	<1
31	10		I	PS	SU	D	H	2K	1–2
32	0	+	H	PS			B	3K	<1
33	10		H	POR	S	D	B	2K	1–2
34	0		H	PU	ORU	D	2H	2	1–2
35	0		I	P		—	H	2K	<1
36	0		H	P		—	B	1K1	1–2
37	0		H	PSU	U	M	H	5K	<1
38	10		H	PS	SCOR	D	B	[illegible]	

39	0	0	0	1000	100	10	1	0	0	1	III−	[illegible]	[illegible]
40	0	0	0	0	0	10	0	1	0	1	I−	III	+
41	0	0	0	0	0	0	0	0	0	0	0	I	−
42	0	0	0	0	0	10	0	0	0	0	10	III	−
43	0	0	0	0	0	0	0	0	0	1	1	II	+
44													
45	0	0	0	0	0	0	0	1	0	0	1	II	+
46	0	0	0	0	0	0	0	0	0	1	1	II	+
47	0	0	0	0	0	0	0	0	0	0	0	I	+
48	0	0	0	0	0	0	0	1	0	1	2	II	+
49	0	0	0	0	0	0	0	1	0	1	2	II	+
50	0	0	0	0	0	20	1	0	1	1	13	III	+
51	0	0	0	1000	0	10	1	1	1	1	1011	V	−
52	0	0	0	0	[illegible]	0	0	0	0	0	0	I	+
53	0	1000	1000	1000	100	10	1	1	1	1	3111	VI	−
54	0	0	0	0	0	10	0	0	0	1	11	III	+
55	0	0	0	1000	100	[illegible]	1	0	0	1	1112	V	+
56													
57	0	0	0	0	0	10	0	0	0	1	11	III	+
58	0	0	0	0	0	0	0	1	0	1	2	II	+
59	0	0	0	0	0	0	0	0	0	1	1	II	+
60	0	0	0	0	0	10	0	0	0	1	11	III	−
61	0	0	0	0	0	0	0	0	0	0	0	I	−
62	0	0	0	0	0	0	0	0	0	1	1	II	−
63	0	0	0	0	0	0	0	1	0	1	2	II	+
64	0	0	0	0	0	10	1	0	1	1	13	III	+
65	0	0	1000	1000	100	10	1	1	1	1	2111	VI	+
66	0	0	0	1000	100	10	1	1	0	1	1111	V	−
67	0	0	0	0	0	0	0	1	0	0	1	II	−
68	0	0	0	0	0	0	0	1	0	1	2	II	+
69													
70	0	0	0	0	0	0	0	1	0	0	1	II	+
71	0	0	0	0	0	0	0	1	0	1	2	II	+
72	0	0	0	0	0	0	0	0	0	1	1	II	+
73	0	0	0	0	0	0	0	0	0	1	1	II	+
74	0	0	0	0	0	0	0	1	0	1	2	II	+
75	0	0	0	0	0	0	0	1	0	1	2	II	+
76	0	0	0	0	0	0	0	0	0	1	1	II	+
77	0	0	0	0	0	0	0	0	0	1	1	II	+
78	0	0	0	0	0	0	0	1	0	0	1	II	−
79	0	0	0	0	0	0	0	0	0	0	0	I	+
80	0	0	1000	1000	100	10	1	0	1	1	2113	VI	−
81	0	0	0	0	0	0	0	1	0	1	2	II	+
82													
83	0	0	0	0	0	0	0	0	0	1	1	II	+
84	0	0	0	1000	100	10	1	0	1	1	1113	V	+
85	0	0	0	0	0	0	0	0	0	1	1	II	+
86	0	0	0	0	0	0	0	1	1	1	3	II	+
87	0	0	0	0	0	0	0	0	0	1	1	II	+
88	0	0	0	0	0	0	0	1	0	0	1	II	+
89													
90	0	0	0	0	0	10	1	1	0	1	13	III	+
91	0	0	0	0	0	0	0	0	0	1	1	II	+

Table 59 (Continued)

Pat No	Electricity	Drain	Running cold water	Toilet indoors	Central heating	Bath or shower	Running hot water	Electric cooking stove	Refrig	Garbage chute	Score	Groups according to score	Fel in home
	Psychosocial factors												
	Home interior factors												
	Home conveniences and equipment												
	0 = Yes 1000 = No	0 = Yes 1000 = No	0 = Yes 1000 = No	0 = Yes 1000 = No	0 = Yes 100 = No	0 = Yes 10 = No	0 = Yes 1 = No	0 = Yes 1 = No	0 = Yes 1 = No	0 = Yes 1 = No		Min Max I = 0 0 II = 1 4 III = 10 14 IV = 100 114 V = 1000 1114 VI = 2000 4114	+ = Yes − = No
1													
2	0	1000	1000	1000	100	10	1	1	1	1	3114	VI	−
3	0	0	0	0	0	0	0	0	0	1	1	II	−
4	0	0	0	0	0	0	0	0	0	1	1	II	+
5	0	0	0	0	0	0	0	0	0	1	1	II	+
6	0	0	0	1000	100	10	1	0	1	1	1113	V	+
7	0	0	0	1000	100	10	0	0	0	1	1111	V	+
8	0	0	0	0	0	0	0	1	0	1	2	II	+
9	0	0	0	0	0	0	0	0	0	1	1	II	+
10	1000	0	1000	1000	100	10	1	1	1	1	3114	VI	−
11	0	0	0	0	0	0	0	0	0	0	0	I	+
12	0	0	0	0	0	10	0	0	0	1	11	III	+
13	0	0	0	0	0	0	0	0	0	1	1	II	+
14	0	0	0	1000	0	10	0	0	0	1	1011	V	+
15	0	0	0	1000	100	10	1	1	1	1	1114	V	+
16	0	0	0	0	0	10	1	0	0	1	12	III	+
17	0	0	0	0	100	10	1	1	0	1	113	IV	+
18													
19	0	0	0	0	0	0	0	0	0	0	0	I	+
20	0	0	0	0	0	10	1	1	1	1	14	III	+
21	0	0	0	0	0	0	0	0	0	0	0	I	+
22	0	0	0	0	0	0	0	0	1	1	2	II	+
23	0	0	1000	1000	100	10	1	1	1	1	2114	VI	−
24	0	0	0	1000	100	10	1	1	0	1	1113	V	−
25	0	0	0	1000	100	10	1	0	1	1	1113	V	−
26	0	0	0	0	0	0	1	1	0	1	3	II	+
27	0	0	0	0	0	0	0	0	0	1	1	II	+
28	0	0	0	0	0	0	0	0	0	0	0	I	−
29	0	0	0	0	0	10	0	0	1	0	11	III	−
30	0	0	0	1000	0	10	1	0	0	1	1012	V	+
31	0	0	0	1000	100	10	1	1	1	1	1114	V	−
32	0	0	0	0	100	10	1	1	1	1	114	IV	+
33	0	0	0	0	0	0	0	0	0	0	0	I	+
34	0	0	0	1000	100	10	1	1	1	1	1111	V	−
35	0	0	0	1000	100	10	1	1	0	1	1113	V	−
36	0	0	0	0	0	0	0	0	0	0	0	I	-
37	[illegible]		[illegible]		100	0	1	1	0				
38													

40	10	0	+	0	+	SOA	—	—	—	
41	0	0	—	0	+	D	—	—	+	S
42	100	0	+	0	+	OA	—	—	+	II
43	100	0	+	0	+	OA	—	—	—	
44						OA	—	—	—	
45	10	100	—	1	—	S	—	—	+	S
46	100	0	+	0	+	OA	—	—	—	
47	10	10	+	0	+	D	—	+	—	
48	100	0	+	0	+	D	—	—	+	SII
49	0	0	—	0	—	S	—	—	—	
50	10	0	+	0	+	D	—	—	+	V
51	0	100		1	+		—	—	—	
52	0	10	—	0	+	D	—	—	+	S
53	0	30	+	0	+	D	—	—	+	IIV
54	10	10	+	1	+	SOA	—	—	—	
55	0	10		1	+	D	—	—	—	
56						D	—	—	+	S
57	0	10	—	10	—	SOA	—	—	—	
58	0	0		0	—	SOA	—	—	—	
59	10	0	—	1	—	D	—	—	—	
60	0	10	—	1	—	OA	—	—	—	
61	10	10	—	0	—	D	+	+	+	IIV
62	0	0	+	0	+		+	+	—	
63	10	100	—	100	—	OA	—	—	+	S
64	10	0	—	0	—	D	—	—	—	
65	0	100		1	+	D	—	—	+	II
66	100	10	+	0	+	D	—	—	—	
67	100	0	+	0	+		—	—	—	
68	10	0	+	0	+	D	+	+	—	
69						D	—	—	+	S
70	100	0	+	0	+	OA	—	—	+	II
71	100	0	+	0	+	OA	—	—	+	S
72	10	0	+	0	+	OA	—	—	+	II
73	10	100	—	100	—	OA	—	—	+	II
74	10	100	+	10	+		—	—	—	
75	10	0	+	1	+	OA	—	—	—	
76	10	10	—	1	+	SD	—	—	+	SII
77	10	0	—	0	—	SOA	—	—	—	
78	100	0	+	0	+	D	—	—	—	
79	0	0	+	0	+	SOA	+	—	+	SII
80	0	10	—	0	+	D	—	—	—	
81	100	0	+	0	+		—	—	+	V
82						D	—	—	—	
83	100	0	+	0	+	OA	—	—	—	
84	0	0	+	1	+	OA	—	—	—	
85	0	100	+	100	+		—	—	+	S
86	0	0	+	1	+		—	—	—	
87	100	10	+	0	+	SOA	—	—	+	S
88	100	0	+	0	+	D	+	—	+	SII
89						SOA	—	—	—	
90	100	0	+	0	+		—	—	—	
91	100	0	—	0	+	OA	—	—	—	

Table 59 (Continued)

Pat No	Psychosocial factors: Home external factors: Unavoidable steps to entrance of home (0 = < 1 steps; 10 = to raised ground floor; 100 = to first floor or higher)	Distance to nearest grocer's shop (metres) (0 = < 300; 10 = 300–999; 100 = ≥ 1000)	Compared with reported max distance able to walk (+ = longer, − = shorter)	Distance to neighbour (metres) (0 = < 10; 1 = 20–49; 10 = 50–299; 100 = ≥ 300)	Compared with reported max distance able to walk (+ = longer, − = shorter)	Economy: Pension (OA = Old age; D = Disability; S = Superannuation; N = None)	Reported economic difficulties (+ = Yes, − = No)	Help necessary not got to extent (+ = Yes, − = No)	Rehab indicated (+ = Yes, − = No)	Goal of rehab (S = Self care; H = House work; V = Vocational activity)
1										
2	0	100	−	1	+	OA	−	−	−	
3	10	0	−	1	−	D	−	−	−	
4	10	100	+	0	+	D	−	−	−	
5	0	0	−	100	−	D	+	+	+	V
6	0	100	−	10	+	OA	−	−	+	S
7	10	10	−	10	−	D	−	−	+	SHV
8	100	0	+	0	+	OA	−	−	−	
9	10	0	+	10	+		−	−	−	
10	0	100	−	1	+		−	−	−	
11	100	0	−	0	−	OA	−	−	−	
12	10	0	−	1	−	SOA	−	−	−	
13	10	100	−	1	+	SOA	−	−	−	
14	10	0	+	1	+	D	−	−	−	
15	0	100	+	1	+	S	−	−	+	HV
16	0	0	+	0	+	D	−	−	+	V
17	10	10	−	1	+	OA	+	−	−	
18						D	−	−	+	SHV
19	10	0	+	0	+	OA	−	−	+	S
20	100	0	+	0	+	OA	−	−	−	
21	100	0	+	0	+	OA	−	−	−	
22	10	0	+	10	+		−	−	+	S
23	0	100	+	10	+		−	−	−	
24	0	10	+	1	+	OA	−	−	−	
25	10	0	+	0	+	OA	−	−	−	
26	100	10	−	0	+	OA	−	−	−	
27	10	0	+	1	+	OA	−	−	+	SH
28	0	0	+	0	+	OA	−	−	−	
29	10	0	−	0	−		−	−	−	
30	0	100	−	10	−	D	−	−	+	S
31	0	100	−	10	+	OA	+	−	+	SH
32	100	10	−	0	−	OA	−	−	−	
33	0	0	+	0	+	D	−	−	+	S
34	100	0	+	0	+	OA	−	−	−	
35	0	10	+	1	+	OA	−	−	−	
36	10	0	+	0	+	OA	−	−	+	S
37	0	100	−	10	+	D	−	−	+	V
38	100	0	−	0	−		−	−	−	
39	10	10	+	1	−	OA	−	−	−	

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Contents

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Abbreviations

A-V	Atrioventricular
$(a\text{-}v)O_2$ difference	Arterio-venous oxygen difference
BSA	Body surface area
CBV	Central blood volume
CHB	Complete heart block
CI	Cardiac index
CO	Cardiac output
E-B	Erlanger-Blackman phenomenon
ECG	Electrocardiogram, electrocardiographic
FEV	Forced expiratory volume in 1 second
FEV %	Forced expiratory volume in 1 second in % of vital capacity
FRC	Functional residual capacity
Hb g %	Hemoglobin in g/100 ml
kpm	Kilopondmeter
LCI	Lung clearance index
M	Mean
mEq/l	Milliequivalents/l
MTT	Mean transit time
MVV_F	Maximal voluntary ventilation at free respiratory rate
PA	Pulmonary artery
$PaCO_2$	Arterial carbon dioxide tension
PaO_2	Arterial oxygen tension
PCV	Pulmonary capillary venous
$\bar{P}_{AO}$	Mean aortic pressure
$\bar{P}_{PA}$	Mean pulmonary artery pressure
$\bar{P}_{PCV}$	Mean pulmonary capillary venous pressure
$\bar{P}_{RA}$	Mean right atrial pressure
PVR	Pulmonary vascular resistance
RA	Right atrium
RV	Residual volume
SD	Standard deviation
SI	Stroke index
SV	Stroke volume
TLC	Total lung capacity
VC	Vital capacity

Introduction

The introduction of artificial pacemakers has proved a major advantage in therapy Patients with Adams Stokes syndrome and complete heart block (CHB) i e the categories from which most pacemaker candidates emanate are often elderly and sometimes bad surgical risks It is therefore important to know the natural history including the prognostic factors when selecting patients for the implantation of a pacemaker A study of 42 patients with Adams Stokes syndrome has been reported in an earlier paper (65) The present account concerns patients with CHB

Malmö is unusually well suited for studies on the frequency and natural history of a disease or symptom such as CHB since the whole town—221 700 inhabitants in 1958—is served by a single hospital Therefore the present study probably comprises almost all of the patients in Malmö known to have CHB The natural history of CHB is presented together with an analysis of various factors in respect of their possible prognostic significance All living patients were examined at a follow up examination

These patients with a slow ventricular rate are probably subject to an unusual load from a sudden change from supine to standing position as well as from physical exercise The patients in best condition were therefore selected at the follow up examination and the hemodynamic results of physical exercise and of a sudden change from supine to standing position were studied in detail as was the possible prognostic significance of the hemodynamic response

Atropine is administered to many patients with CHB in an attempt to increase the pulse rate and inhibit Adams Stokes attacks The hemodynamic study ended therefore with an investigation of the effect of atropine given intravenously The results were also analysed with regard to the possible prognostic value of an atropine test

Since many cardiotropic agents operate through changes in heart rate patients with an artificial pacemaker and consequently a constant ventricular rate may react in an unusual manner to drug administration These patients are also interesting from a purely scientific point of view as the chronotropic effect of a drug on the ventricles is eliminated Many drugs lend themselves to such a study Because the chronotropic effect of digitalis is considered to be an important

Material and methods Clinical and prognostic study

A Criteria

The *criteria of complete heart block* (CHB) in this study are independence of atrial and ventricular rhythms as established in the electrocardiogram (ECG) and failure of the ventricles to respond to any sinoatrial impulse and a ventricular rate slower than the atrial (100)

A CHB verified electrocardiographically at the follow up examination or in the last ECG before death has been termed a *constant CHB* whether or not the patient had previously shown one or more episodes of CHB An earlier CHB on one or more occasions but not at follow up or in the last ECG before death has been termed a *transient CHB*

B Material

Clinical study

The electrocardiographic records of the Heart Laboratory at the Department of Medicine Malmo General Hospital were found to include 204 patients with a diagnosis of CHB during the years 1951—1964 Of these patients 134 had a constant CHB while 70 were classified as transient The hospital records of all 204 patients were perused and an analysis was made of the clinical, electrocardiographic and hemodynamic data presented in chapter III (tables 1 2 5—9 and figures 2 and 6) Many patients had had more than one ECG or blood pressure recorded in which case a representative record or value was used

The 55 patients (fig 1) alive at follow up were given a physical examination at which an ECG was recorded Furthermore a detailed history was taken Certain aspects of these living patients are presented in chapter III (tables 3 4 and figures 3—5)

Prognostic study

In 11 of the 204 patients the CHB had first appeared in 1950 or earlier Since other patients with CHB were no doubt admitted and died in 1950 or earlier with the result that their ECGs are not found in the files of the Heart Laboratory these 11 patients constitute a selection and if included would give an unduly favorable prognosis for patients with CHB Consequently only the 193 patients diagnosed during the years 1951—1964 have been included in the prognostic study which is presented in chapter IV (tables 10—17 and figures 7—14)

The files of the Heart Laboratory

property of this drug the hemodynamic effect at rest and during exercise has been investigated before and after digitalis administration to patients with an artificial pacemaker

contain all the ECG records of the hospital except those from the Department of Infectious Diseases and during 1962—1964 from the Department of Pediatrics The files from the Department of Pediatrics were checked and no patients with CHB were found The Department of Infectious Diseases does not have a central file but it is common practice that patients with CHB are referred to the Department of Medicine for consultation and an ECG is then taken which is included in the files of the Heart Laboratory

Many ECGs from private practitioners are taken in the Heart Laboratory while some private practitioners with special interest in cardiology record ECGs of their own These colleagues were contacted and kindly put their ECGs with CHB at my disposal Only two patients with CHB were found in this way indicating that the great majority of ECGs with CHB are to be found in the files of the Heart Laboratory As Malmö (a town of 221 700 inhabitants in 1958) is served by only one hospital it may be concluded that the material in this study probably includes almost all of the patients in Malmö known to have CHB

C Methods

Pertinent data on the deceased patients were extracted from the hospital records

The clinical examination of the living patients included a detailed *history* according to a standard form a *physical examination* and a 12 lead ECG leads I II III aV$_R$ aV$_L$ aV$_F$ V$_1$ V$_2$ V$_3$ V$_4$ V$_5$ and V$_7$ were recorded with a four channel direct writing ink jet electrocardiograph [2] A hemoglobin value was determined photometrically [3] The patients were checked for the presence of proteinuria and glucosuria with Albustix and Clinistix (Ames) If possible a spirometry was done and a *roentgenogram of the heart* was taken Heart volume with the patient in the standing position was determined according to Jonsell (69) Relative heart volume i e ml per square meter body surface area (ml/sq m BSA) was estimated according to Lysholm et al (89)

The *lung function test* included vital capacity in litres (VC) forced expiratory volume in 1 second in litres (FEV$_{1.0}$) forced expiratory volume in 1 second as a percentage of vital capacity $\left[\frac{FEV_{1.0}}{VC}\times 100\right.$ (FEV %), for technique and normal values see Berglund et al (10)] maximal voluntary ventilation at free respiratory rate (MVV$_F$) functional residual capacity in litres (FRC), total lung capacity in litres [TLC for technique and normal values see Grimby and Söderholm (54)] and lung clearance index [LCI (3)] with normal values obtained from Bouhuys (16)

If possible an *exercise test* was done with the patient in the sitting position on an electrodynamically braked bicycle ergometer The work load at maximal intensity was determined ac

[2] Mingograph 42 B Elema Schonander Stockholm Solna

[3] Janson 3 Ljungberg & Co Stockholm

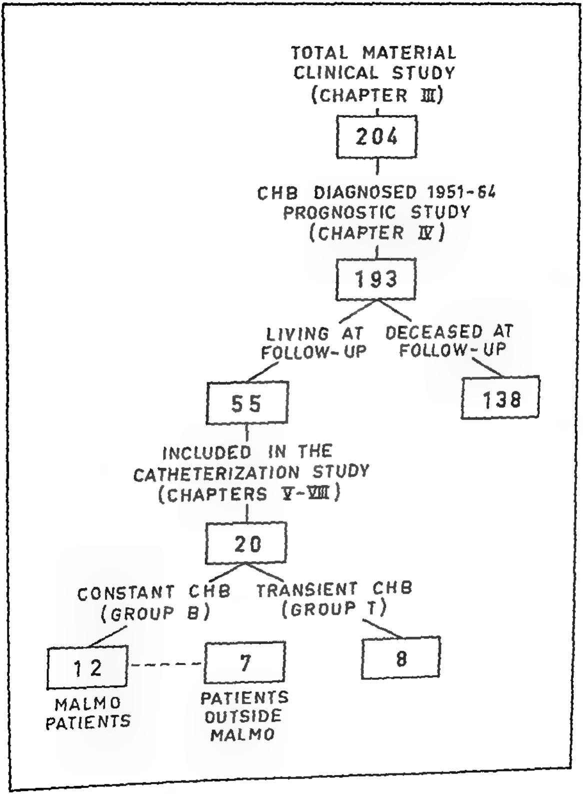


Fig 1 Presentation of the material See further the text

Clinical aspects of complete heart block

A. Frequency

In the present material there were 134 patients with constant and 70 patients with *transient* complete heart block (CHB). The 204 patients with CHB were extracted from 144 186 electrocardiograms (ECG) 1.4 ‰ recorded during 1951—1964 on 59 847 patients (3.4 ‰). Assuming that most patients with CHB in Malmö have ECGs in the Heart Laboratory files the prevalence of CHB in Malmö with 245 565 inhabitants on December 31, 1964 works out at 0.22 ‰. Calculating with the 193 patients in whom the diagnosis was first made in the period 1951—1964 the incidence is 14 patients per year or 6.3 patients per 100 000 inhabitants per year.

Hanssen (58) found CHB in 66 patients of 59 000 (1.1 ‰) admitted during 1930—1945 to the medical clinics of the municipal hospitals of Oslo where the population was about 270 000, which means 2.4 patients per 100 000 inhabitants per year. Wright et al (137) observed 90 patients with CHB in 49 000 inhabitants in Galveston, Texas (1.8 ‰) and Wyss et al (138) 54 in 24 000 Swiss patients during 1942—1956 (2.3 ‰). This steady chronological increase suggests that the higher rate reflects a growing use of ECG recordings rather than any geographical difference. If this assumption is correct the high figure (3.4 ‰) in the Malmö material indicates that a comparatively large proportion of all patients with CHB in Malmö has been collected.

Health surveys have not included enough people to yield reliable values on the frequency of CHB in the total population for comparison with the above mentioned figures. Johnson et al (67) reported a sizeable material of 67 375 apparently healthy male fliers and found only one case of CHB but this was a selected group.

Instead of the number of patients many authors quote the number of ECGs from which the CHBs have been collected. Ellis (37) found 40 patients with CHB in 7 515 ECGs (5.3 ‰), Ide (63) 69 in 25 286 (2.7 ‰), Rowe and White (106) 350 in 160 000 (2.2 ‰), Kempf (76) 25 in 15 000 (1.7 ‰), Meyer Leddin (97) 29 in 27 300 (1.1 ‰), Cardenas et al (25) 103 in 60 000 (1.7 ‰) and Wyss et al (138) 54 in 66 000 (0.8 ‰). The corresponding figure in the Malmo material was 1.4 ‰. The chronological fall of the CHB rate in these materials may reflect a steady rise in the number of

cording to Strandell (125), i e as the heaviest load at which the patient worked for six minutes with an increment proportional to the completed part of the six minute period at the load above this (a patient working for six minutes at 300 kpm/min and two minutes at 600 kpm/min was calculated to have a work load of $300+\frac{2\times 300}{6}=400$ kpm/min at maximal working intensity) Individual observations for the patients participating in the catheterization study (see fig 1) are given in the Appendix table A

Conventional *statistical methods* were used with conventional significance limits *0 05>P>0 01 for probably significant*, 0 01>P>0 001 for significant and P<0 001 for highly significant

Table 1 *Total material of 204 patients with complete heart block (CHB) used for the clinical study The age groups refer to the age at diagnosis of CHB Figures in brackets show the number of women in the group In age group 85—89 there are thus 1 man and 4 women with unknown etiology*

Age	Unknown etiology	Acute myocardial infarction	Non acute coronary heart disease	Hypertension	Rheum heart disease	Digitalis intoxication	Miscellaneous	Total
15—19	—	—	—	—	1	—	1 (1)	2 (1)
20—24	1 (1)	—	—	—	—	—	—	1 (1)
25—29	1 (1)	—	—	—	—	1 (1)	—	2 (2)
30—34	1	—	—	—	—	—	1	2
35—39	—	—	—	—	—	—	2 (1)	2 (1)
40—44	1	—	—	—	1 (1)	—	2 (1)	4 (2)
45—49	1	3	—	—	2 (1)	—	—	6 (1)
50—54	—	7 (1)	1 (1)	—	3	—	2	13 (2)
55—59	2 (1)	5	1	—	1	1	1 (1)	11 (2)
60—64	8 (4)	7 (3)	1	—	—	1 (1)	1	18 (8)
65—69	6 ([illegible])	1[illegible] (3)	5 (1)	2 (2)	—	1 (1)	4 (2)	30 (11)
70—74	17 (8)	12 (4)	2	3 (1)	1	1 (1)	1	37 (14)
75—79	17 (4)	9 (5)	8 (1)	4 (4)	—	3 (2)	3 (1)	44 (17)
80—84	3	4	4 (1)	3 (3)	—	4 (2)	1	19 (6)
85—89	5 (4)	3 (1)	2 (1)	—	—	2 (1)	—	1[illegible] (7)
90—94	1	—	—	—	—	—	—	1
Total	64 ([illegible])	62 (1[illegible])	24 ([illegible])	12 (10)	9 (2)	14 (9)	19 (7)	204 ([illegible])
In % of grand total	31.4 (33.3)	30.4 ([illegible]2.7)	11.8 (6.7)	[illegible]9 (13.3)	4.4 (2.7)	6.9 (12.0)	9.3 (9.3)	100.0 (100.0)

(139) 7 % Bruns et al (20) 3 % and Brown and Rognoni (18) 0 % The patients classified as unknown etiology in table 1 displayed no signs of ischemic hypertensive or rheumatic heart disease and digitalis was not given This classification was justified by autopsy findings in 31 of the 47 deceased patients no signs of coronary occlusion were detected and only slight to moderate atherosclerosis in the coronary arteries Furthermore coronary arteriography in a patient (case 3 in the Appendix table L) not included in this material but belonging to the same etiological group showed only minute irregularities in the coronary arteries

The concept that in some patients with CHB no clinical etiology can be found is supported by a recent paper by Zion and Bradlow (142) and Zoob and Smith (143) reporting the finding of a large "primary" group discussed the possible etiology but ruled out ischemic and hypertensive heart disease rheumatism and syphilis In many papers Lenègre has described detailed microscopic studies of the interventricular septum in patients with CHB

ECGs recorded in patients in whom heart disease is suspected

These tendencies for CHBs as a percentage of all ECGs to decrease with time and for CHBs as a percentage of the patients in whom ECG has been recorded to increase with time could support the assumption that the Malmo material contains the majority of CHBs occurring in patients visiting the hospital, thus the former percentage for the Malmo material was comparatively low (1 4 ‰), while the latter was high (3 4 ‰)

B Classification of cases

The total material of 204 patients with CHB has been broken down in table 1 by dominant disease, sex and age at electrocardiographic discovery of CHB The diagnosis of CHB was always verified electrocardiographically according to the criteria in chapter II

It would of course be more correct to speak of dominant diseases or etiologies of CHB since more than one disease may contribute to the final result This is especially the case in elderly patients For example, the patients in the group *digitalis intoxication* in table 1 had a cardiac disease such as rheumatic, hypertensive or *ischemic heart disease* with cardiac decompensation which was the indication for digitalis administration The assessment of the *dominant etiology* has been made from hospital records autopsy findings and/or personal examination This grouping is practical and a further justification for it is that the prognosis is different between these groups, as are the clinical and electrocardiographic characteristics

The criteria used for diagnosing *acute myocardial infarction* were those described by Sievers (116) with the addition of enzymic data Patients classified as *nonacute coronary heart disease* all had anamnestic and/or electrocardiographic signs of coronary insufficiency Patients having myocardial infarction or significant coronary arteriosclerosis at autopsy were also included in these groups in accordance with the classification system used by Penton et al (102) Inclusion in the *hypertension* group required a systolic blood pressure of 200 mm Hg or more or a diastolic of 100 or more and no infection in connection with the beginning of CHB The patients also had subjective or objective symptoms of their hypertension or were treated for it These high blood pressure values were chosen in view of the high mean age in this material Patients were referred to the *rheumatic heart disease group* if they had valvular heart disease of rheumatic origin or the hospital record diagnosis was acute rheumatic fever Jones modified criteria were used for this diagnosis (56)

As table 1 shows, ischemic heart disease, i e acute myocardial infarction and coronary heart disease, predominate However the percentage of patients with *unknown etiology* is comparatively high, 31 % in contrast to many other materials e g those published by Ide (63) who reported 3 % with unknown etiology, Penton et al (102) 7 % Rowe and White (106) 3 % Gilchrist (47) 2 %, Wyss et al

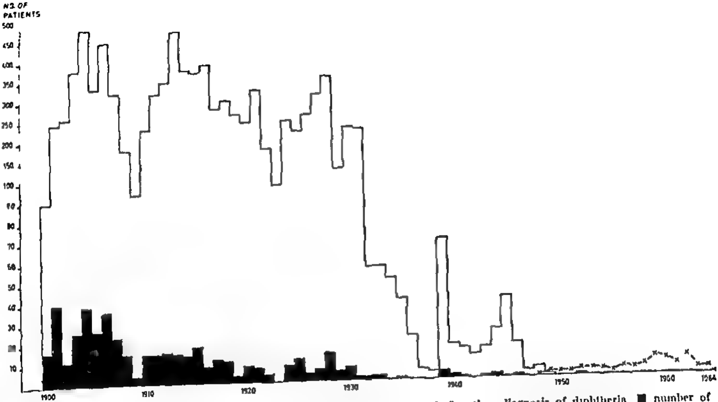


Fig. 2 Number of patients admitted to the Department of Infectious Diseases in Malmö with a diagnosis of diphtheria ■ number of deaths caused by diphtheria x x x number of patients with completeheart block of unknown etiology

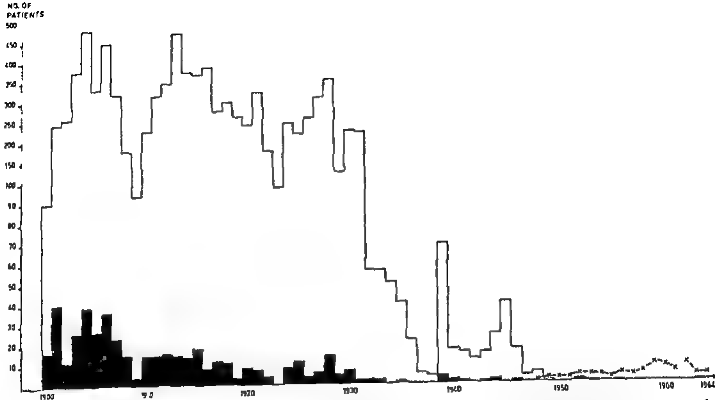
In one report on 44 observations, of which 41 had CHB, he (84) found a pronounced coronary sclerosis in 12 cases, slight in a further 12 and complete absence in 20, while in an etiologic study on 552 cases Moreau et al (99) found 150 cases, 27 %, of undetermined origin Landegren and Biorck (82) have given a detailed review of different possible etiologies of CHB

Some histological studies have been made of the interventricular septum in patients with CHB of unknown etiology Lenègre (83) pointed out that in the 'primary' group the etiology is not an ischemic cardiopathy Lev (86) considered that perhaps the most common cause of permanent complete A V block is sclerosis of the left side of the cardiac skeleton producing disruptive lesions of the A V node, bundle or beginning of the bundle branches Biss (14) suggested from a study of five cases that the senile dilatation of the aortic ring results in mild aortic incompetence with a regurgitant stream which causes fibrosis of a portion of the interventricular septum and hence involving the underlying bundle of His by compression or invasion Rossi (105) described a patient with chronic lymphangitis causing CHB It seems then that there is more than one cause of CHB in the unknown group (85) More and detailed histopathological studies including serial cutting of the interventricular septum are needed to elucidate these problems

In earlier materials the etiology of CHB has in most patients been given as arteriosclerotic heart disease This was also the case in the Malmo material although usually not to the same extent as table 1 shows, ischemic heart disease, as acute myocardial infarction and nonacute coronary heart disease amounted to 42 %, this is the same figure as given by Penton et al (102) while that published by Wyss et al (138) is 56 % The proportion of unknown etiology, 9 out of 32 patients, reported by Zion and Bradlow (142) was similar to that in the Malmö material In the material published by Zoob and Smith (143) CHB of unknown etiology was much more predominant, constituting 30 out of 51 patients, while only 12 patients were classified as having ischemic heart disease

It is noteworthy that no clear cut cases of *congenital CHB* were observed in the present series In a joint study Michaëlsson (98) collected 178 cases with CHB fulfilling Yater s (140) criteria for congenital CHB and Campbell and Suzman (22) stated that congenital heart block is probably more common than has been thought The higher ventricular rate in congenital CHB than in acquired CHB even with increasing age might be a reason for overlooking the diagnosis Conversely other reports for instance by Yater (139) indicate that congenital CHB is not common and Campbell (24) has subsequently modified his opinion Further studies are needed to clarify the incidence and prevalence of congenital CHB

Diphtheria has been reported to be a common cause of late CHB where no other etiology is apparent (21) This has been contradicted among



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others by Jones and White (68) who reexamined 100 patients at least five years after severe or moderately severe diphtheria but found no case of CHB. In the present material 4 patients in the unknown etiology group and 4 in the rest of the material had a history of diphtheria. If diphtheria were a cause of CHB one would expect a variation in the incidence of CHB of unknown etiology similar to the variation in incidence of diphtheria. As shown by fig. 2 there is no such conformance. Furthermore, none of the patients admitted to hospital in Malmö with a diagnosis of diphtheria in 1932 and later have appeared in the present unknown etiology group. It thus seems most improbable that diphtheria is a common causative factor of late CHB.

The *miscellaneous* group in table 1 consists of 19 patients. In ten of these, CHB was probably elicited by a myocarditis, two cases were of luetic origin, one appeared during a sepsis caused by enterococci, one in connection with morbus Reiter, one was caused by a sarcoidosis and one by a collagen disease, two cases appeared in connection with cholecystitis and one during delirium tremens. The nature of the myocarditis in the 10 cases varied. One was possibly a listerella myocarditis. In several patients the CHB appeared during a mild and initially uncomplicated infection. Case No. 1 below is an example of this pattern. Cases 2 and 3 had a morbus Reiter and sarcoidosis, respectively.

Case 1, ♂, born 1915 (case 25 in the Appendix, table A). Well until September 23, 1959, when he suddenly developed nausea and vomited the day after his daughter had shown similar symptoms. His wife was taken ill the following day. Both these members of the family recovered but the patient was tired and diarrhea remained. On October 7 he fainted. Two days later he was unusually tired and short of breath. He was admitted to hospital on October 17. No signs of cardiac decompensation were found. Blood pressure was 190/90 and ECG showed CHB with a ventricular rate of 48/min and a QRS duration of 0.08 secs. X-ray of the heart was normal with a volume of 850/450 ml/sq m BSA. No fever. Laboratory data were normal except a white cell count of 11,700/cmm and 80.5 % neutrophils in the blood smear. Serological reactions were normal as was a fecal culture. Electrocardiographically the CHB changed to 2 : 1 block. Wenckebach periods were recorded and on November 5 an A-V block of the first degree appeared. On December 21 the ECG was quite normal. He has felt quite well ever since his discharge from hospital.

Case 2, ♂, born 1927 (case 26 in the Appendix, table A). First bout of joint pain occurred in 1944. In 1953 a purulent secretion appeared from the urethra and some days afterwards joint pains. After five similar bouts he was admitted to the medical clinic in Malmö in 1958. Sedimentation rate was 77 mm/hour. X-ray of the heart was normal with a volume of 690/350 ml/sq m BSA. ECG was normal. He was given corticosteroids and discharged in a good condition. He had no signs of conjunctivitis but was diagnosed as morbus Reiter. A new bout occurred in May 1962. In October 1962 joint pains appeared again. Two weeks after the pains began he suddenly became tired and short of breath but did not faint. He was admitted to the medical clinic in Malmö where CHB was diagnosed. QRS duration 0.10 secs. The pulse rate was 32/min, blood pressure 130/75. No fever. Laboratory findings were normal apart from an initial sedimentation rate of 15 mm/hour. Antistaphylolysin titre was slightly increased but other serologi-

cal reactions including gonococc complement binding reaction were normal Cultures for gonococci were negative X ray of the heart was normal with a volume of 640/310 ml/sq m BSA He was given corticosteroids and improved CHB was followed by Wenckebach periods and later an A V block of the first degree which persisted at follow up He feels quite well

Case 8 ♀ born 1901 well except for migraine and a gastric ulcer experienced her first fainting attack three weeks before admittance to the medical clinic in 1959 ECG showed CHB and bundle branch block of varying types She was given ephedrine Three days after the beginning of ephedrine treatment ECG showed sinus rhythm with a normal P R interval and right bundle branch block A roentgenogram of the heart was normal but diffuse bronchiectatic changes were found in the right upper lung lobe no hilus changes were found Serum cholesterol was 340 mg/100 ml and the sedimentation rate 12 to 16 mm/hour The tuberculin test (1 mg) was negative She was discharged with atropine and sedatives but experienced several syncopal attacks She died suddenly two months after leaving hospital *Autopsy* showed sarcoid changes with a pronounced involvement of the left ventricle and left atrium and especially of the interventricular septum The lymph glands of the lung root were also involved by the sarcoid but only slight changes were found in the lung parenchyma The roentgenologically verified changes in the upper lung lobe were interpreted as sequela of lung tuberculosis Apart from the heart and lungs sarcoid changes were found in a few lymph glands in the groins but not elsewhere

C Age and sex distribution

Table 1 shows that CHB is a symptom of old age with the largest number of diagnoses being made in the eighth decade although 19 patients 9 % of the total material were in fact less than 50 years old when CHB was discovered The age range is 15—91 years with a mean of 68 3 years This agrees with reports by Ide (63) Meyer Leddin (97) and Zion and Bradlow (142) who also found the bulk of patients to be in the eighth decade and Ellis (37) who found 10 out of 40 patients in the eighth decade but also 10 patients in the sixth decade Karni and Werkö (71) observed 7 out of 24 patients in the eighth decade but also 7 patients in the sixth decade Grappe et al (51) reported an almost equal distribution between patients in the seventh and eighth decade in their material while Penton et al (102) and Cardenas et al (25) observed a predominance in the seventh decade

There is little difference in *mean age of the different groups* in the case of unknown etiology myocardial infarction coronary and hypertensive heart disease and digitalis intoxication i e 70 3 67 7 74 2 75 7 and 73 6 years respectively The mean age is lower in the miscellaneous group 57 1 years and lowest for rheumatic heart disease 47 7 years The figures reported by Penton et al (102) are lower in most groups with a mean age of 62 5 years for the acute myocardial infarction group 63 5 for the coronary heart disease group and 44 5 for the group with undetermined etiology Zoob and Smith (143) reported an average age of 67 years for their primary group which is similar to the average of 70 3 found in the unknown group in the present material

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Table 2 *Cause of consultation in 204 patients with complete heart block*

Cause of consultation	No of patients
Low heart rate	9
Syncope	44
Other cardiac symptoms	102
Noncardiac disease	49

tacks has been suggested by McLemore and Levine (93) This concept is supported by the disappearance of Adams Stokes attacks in one patient after cholecystectomy (64) While this connection may exist in some cases it is not apparent in a larger material among the patients with unknown etiology in the present material the percentage of those with syncope among those known to have gall bladder disease did not differ from the percentage of patients with syncope in the total group (75 % and 77 % respectively)

There was also a comparatively high percentage of various diseases of the urinary tract in the group with unknown etiology (10 out of 64) and in the miscellaneous group (3 out of 19) Of the 62 patients with acute myocardial infarction 12 had diabetes mellitus compared with only 3 out of 64 in the group with unknown etiology and 2 out of 24 with coronary heart disease

Since the slow heart rate with high pulse pressure in patients with CHB may exert an undue strain on the vessels a study was made of the occurrence of *myocardial infarction and cerebral lesions* after the beginning of CHB Disregarding the group in which acute myocardial infarction caused CHB (see table 1) no cases of myocardial infarction were observed while seven patients had a diagnosis of cerebral lesion Six of these had a constant CHB while one belonged to the transient group The ratio of patients with constant and transient CHB in this part of the material with the myocardial infarction group excluded was 102 40 Only in two patients did the cerebral lesion appear in connection with the onset of CHB in the other patients the interval varied between two months and two years The patient with a transient CHB developed the cerebral lesion after a syncopal attack as was the case in two of the patients with constant CHB

Since it proved difficult to get satisfactory data on other pertinent clinical symptoms the items discussed below (before the ECG findings) concern only the 55 patients who were alive at follow up (fig 1) and who were all examined by myself It must be remembered in the following discussion that these 55 patients presented in table 3 are a selection and hence not representative of the entire CHB material

It is remarkable how seldom *angina pectoris* occurred in patients with CHB Excluding the myocardial infarction group from the 55 patients alive at follow up only four experienced angina pectoris after the onset of CHB and these had all had this symptom previously three of them belonged to the coronary heart disease group and one to the digitalis intoxication group There was thus no case

It is obvious from the *sex distribution* in table 1 that the male patients dominate the total material and all groups except hypertension and digitalis intoxication Although Fatzer (38) reported female preponderance in the total material, males predominate in most studies in numbers over females (20, 23, 37, 53, 58, 63, 74, 102, 137, 138)

It is noticeable (see table 1) that the male female quotient among patients with unknown etiology is smaller than among patients with acute myocardial infarction or coronary heart disease In a report by Penton et al (102) the male female quotient is equal to 1 for the group with undetermined etiology and higher than 1 for the group with ischemic heart disease Similar findings have been published by Zion and Bradlow (142) The two patients with CHB of unknown etiology in Graybiel and White's series (53) were both females and in a study of Zoob and Smith (143) the male female ratio in the primary group was 20 10 while in the ischemic group it was 8 0 The different sex ratios favor the concept that the groups unknown etiology and ischemic heart disease represent different entities

Summarizing, a material of 204 patients with CHB extracted from the Heart Laboratory files for 1951—1964 has been analyzed The prevalence of CHB in Malmö in 1964 is calculated to 0 22 ‰ and the incidence to 6 3 patients per 100,000 inhabitants per year The different etiologies are given in *table 1* ischemic heart disease, i e acute myocardial infarction and coronary heart disease, predominated but patients with unknown etiology constituted one third of the material An analysis of the frequency of diphtheria showed that this disease could be excluded as a common cause of CHB in the group with unknown etiology The mean age for the total material was 68 3 years, range 15—91 years Males were more numerous than females in all except the hypertensive and digitalis intoxication groups

D Symptomatology

Only in nine patients was the *cause of consultation* the slow pulse rate (table 2) Syncope was the cause in 44 patients, other cardiac symptoms in 102, while in 49 cases CHB was detected when the patient consulted a doctor for a non cardiac disease Wyss et al (138) reported that half of their patients consulted a doctor because of symptoms which could be referred to the CHB while in the other half CHB was discovered while the patient was being treated for some other cardiovascular disturbance such as cardiac decompensation, hypertension or angina pectoris

Concerning the *previous history* it is striking that 16 of the 64 patients with unknown etiology had gall bladder disease This complaint was also comparatively common in the non acute coronary heart disease group (4 out of 24 patients) and in the miscellaneous group (4 out of 19 patients) while it was present in only 7 of the remaining 97 patients A connection between gall bladder disease and Adams Stokes at

Table 4 *Occurrence of cardiac decompensation in the patients living at follow up Only 50 patients are included since two patients were decompensated already before the beginning of CHB and in three patients no reliable history could be taken*

Diagnosis	Yes		No	
	Constant	Transient	Constant	Transient
Unknown etiology	[illegible]	1	9	2
Acute myocardial infarction	—	—	—	11
Nonacute coronary heart disease	1	1	2	1
Hypertension	—	—	—	—
Rheumatic heart disease	—	—	2	2
Digitalis intoxication	—	1	—	2
Miscellaneous	2	—	4	4

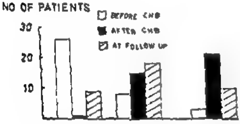

Fig 3 Functional capacity classified according to the criteria of the New York Heart Association in the patients living at follow up before complete heart block (CHB) just after the onset of CHB and at follow up examination Only patients who could be evaluated just after the onset of CHB are included

with CHB was reduced which is apparent from their histories and will also be demonstrated in chapter VII Fig 3 which is constructed in the same way as fig ■ shows the patients functional capacity classified according to the criteria of the New York Heart Association before CHB just after CHB has been established and at follow up It will be seen that functional capacity decreased as reflected in the shift away *from* class I This tendency is most pronounced just after *CHB has been established* At follow up there is a certain reversal although preCHB figures are never reached As shown in chapter VII the work load at maximal working intensity is lower than the value for healthy old men This favors the concept that the time just after the onset of CHB is most critical and that later there is an adaptation to the decreased *ventricular rate*

The functional capacity can also be estimated from whether patients *had to change occupation* because of the CHB It was found that among the 55 patients alive at follow up 9 had changed their occupation while 23 had not The rest had already retired by the onset of CHB

Figure 4 shows the *main symptoms produced by exercise* in the living patients before CHB just after its onset and at follow up The *distribution between* fatigue and dyspnea was similar before and after CHB It was striking that in some patients with CHB the first symptom during the ergometer

Table 3 The 55 living patients with complete heart block examined at the follow up Figures in brackets show the number of women See further the legend to table 1

Age	Un known etiology	Acute myo cardial infarc tion	Non acute coronary heart disease	Hyper tension	Rheum heart disease	Digi talis intoxi cation	Miscel laneous	Total
15—19	—	—	—	—	1	—	1 (1)	2 (1)
20—24	—	—	—	—	—	—	—	—
25—29	—	—	—	—	—	—	—	—
30—34	—	—	—	—	—	—	1	1
35—39	—	—	—	—	—	—	2 (1)	2 (1)
40—44	1	—	—	—	—	—	2 (1)	3 (1)
45—49	1	1	—	—	1 (1)	—	—	3 (1)
50—54	—	1	—	—	1	—	1	3
55—59	1	1	—	—	—	—	—	2
60—64	2	2 (1)	—	—	—	1 (1)	—	5 (2)
65—69	3 (1)	3	1	—	—	—	3 (1)	10 (2)
70—74	6 (3)	2 (1)	1	1	1	1 (1)	1	13 (5)
75—79	4	—	2	—	—	—	—	6
80—84	—	—	1	—	—	2 (1)	—	3 (1)
85—89	—	1 (1)	—	—	—	1 (1)	—	2 (2)
Total	18 (4)	11 (3)	5 (0)	1 (0)	4 (1)	5 (4)	11 (4)	55 (16)
In % of grand total	32.7 (25.0)	20.0 (18.8)	9.1 (0)	1.8 (0)	7.3 (6.2)	9.1 (25.0)	20.0 (25.0)	100.0 (100.0)

of the functional angina pectoris described by *Froment et al* (41) The results in the Malmö material is in conformance with reports by *Graybiel and White* (53), *Penton et al* (102) and *Wyss et al* (138) who also observed no or few cases with angina pectoris after CHB debute

Cardiac decompensation (table 4) on the other hand was more common (22 %) Only 50 patients are included in the table because two were decompensated before the beginning of CHB and three could not provide a reliable history This figure of 22 % should be compared with the 40 % reported by *Penton et al* (102) Cardiac decompensation was not found in the present material in patients who had had a myocardial infarction Among the patients with constant CHB one third of those with unknown etiology non acute coronary heart disease or miscellaneous diagnoses were decompensated while both of the patients with rheumatic heart disease were not

Thirty five patients (64 %) had no *subjective cerebral symptoms* after the onset of CHB while five complained of dizziness four of forgetfulness and one of impaired ability to concentrate The rest had various symptoms such as tiredness and anxiety

The *functional capacity* of patients

Summarizing the cause of consultation among the 204 patients with CHB was syncope in one quarter and other cardiac symptoms in half. Gall bladder disease was a frequent finding. Myocardial infarction was not seen after the beginning of CHB but cerebral lesions occurred in seven patients.

The fifty five patients alive at follow up were analyzed with respect to different symptoms after the onset of CHB. Angina pectoris was not observed, cardiac decompensation occurred in 22 %. The functional capacity was reduced and one fourth of the patients of working age had to change their occupation because of the CHB. The functional capacity showed an improvement at follow up compared with the findings just after the onset of CHB indicating an adaptation to the low ventricular rate. A similar result was found for the number of orthostatic reactions on these three occasions.

E. Electrocardiographic findings

Table 5 shows that the *atrial rate* differed somewhat in the different groups. Patients with acute myocardial infarction, hypertension or digitalis intoxication had a higher atrial rate compared with patients with unknown etiology or coronary or rheumatic heart disease while the miscellaneous group showed a slightly lower rate.

The *ventricular rate* also varied with the diagnosis (table 6). The lowest rate was found in patients with an unknown etiology and the highest in those with digitalis intoxication or

Table 5. *Mean values of atrial rate in beats/min in patients with complete heart block. Only 183 of the 204 patients are included because 19 had atrial fibrillation and 2 had atrial flutter.*

Diagnosis	Mean	No of patients
Unknown etiology	89.2	62
Acute myocardial infarction	95.7	60
Nonacute coronary heart disease	90.5	19
Hypertension	96.1	9
Rheumatic heart disease	90.8	8
Digitalis intoxication	94.3	8
Miscellaneous	85.6	17
Total	91.8	183

myocardial infarction. Penton et al (102) and Rowe and White (106) also reported the highest ventricular rate in the digitalis intoxication group. A high ventricular rate in patients with acute myocardial infarction and CHB is a usual finding and Gilchrist (47) pointed out that there is consequently a danger of the CHB in these patients being overlooked.

The ventricular rate in the total material ranged between 17 and 84 beats/min with a mean of 43/min. It thus seems that CHB is not necessarily associated with a slow ventricular rate. This was also pointed out by Penton et al (102) and Ide (63) who found maxima of 97/min and 103/min respectively.

Table 6 shows that the bulk of the patients with a ventricular rate above 50/min had a myocardial infarction while ventricular rates of 30/min or below are dominated by patients with an unknown etiology.

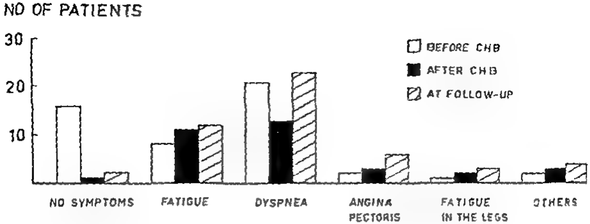

Fig 4 Main symptoms produced by exercise in the patients living at follow up before complete heart block (CHB) just after the onset of CHB and at follow up examination

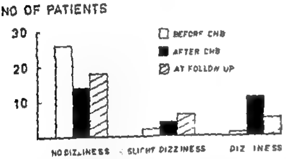

Fig 5 Reaction to a sudden change in posture from a supine to standing position in patients living at follow up before complete heart block (CHB) just after the onset of CHB and at follow up examination Only patients who could be evaluated just after the beginning of CHB are included

test which was performed at follow up on as many patients as possible was fatigue and pain in the legs In the total material however the percentage of leg pains was no greater than in Strandell s (124) normal subjects

The patients subjective *reaction to a sudden change in posture* from a supine to standing position was generally normal before CHB with only a few patients experiencing dizziness Just after the onset of CHB the percentage feeling dizziness rose and the severity of the orthostatic reaction increased—one patient even fainted At follow up there was some improvement but not to the preCHB figures

It was not possible to evaluate the reaction just after the onset of CHB in some patients However confining the study to those patients who could be evaluated at this stage gives a similar result, as is apparent from fig 5 Before CHB only three out of 26 patients (12 %) experienced dizziness when they suddenly changed from a supine to a standing position This figure rose to 52 % just after CHB had been established but at follow up there was an improvement only 38 % experiencing dizziness As in the case of functional capacity there seems to be a gradual adaptation of the circulatory system to the slow ventricular rate A detailed hemodynamic study of the changes during an orthostatic test in patients who have had a prolonged CHB is given in chapter VI

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Table 6 shows that the bulk of the patients with a ventricular rate above 50/min had a myocardial infarction while ventricular rates of 30/min or below are dominated by patients with an unknown etiology.

Table 6 *Ventricular rate in beats/min in patients with complete heart block*

Ventricular rate beats/min	Unknown etiology	Acute myocardial infarction	Non acute coronary heart disease	Hypertension	Rheum heart disease	Digitalis intoxication	Miscellaneous	Total
0—10	—	—	—	—	—	—	—	—
11—20	1	—	1	—	—	—	—	2
21—30	15	4	1	—	—	1	—	21
31—40	24	19	8	4	2	4	7	68
41—50	20	19	8	7	[illegible]	6	8	74
51—60	2	16	3	1	—	[illegible]	4	28
61—70	1	2	3	—	1	—	—	7
71—80	1	2	—	—	—	—	—	3
81—90	—	—	—	—	—	1	—	1
Mean	38 3	46 0	44 4	42 7	44 9	47 1	43 6	43 0/204

Table 7 *Occurrence of a positive Erlanger Blackman phenomenon in patients with complete heart block. Only the 116 patients not treated with vagolytic or sympathomimetic agents are included*

	Unknown etiology	*Acute myocardial infarction*	*Non acute coronary heart disease*	*Hypertension*	*Rheum heart disease*	*Digitalis intoxication*	*Miscellaneous*	*Total*
E B	17	8	3	1	4	0	5	38
No E B	24	23	9	4	3	7	[illegible]	78

Atrial fibrillation in combination with CHB was observed in 19 and *atrial flutter* and CHB in 2 of the 204 patients. Penton et al (102) reported a still higher frequency of atrial fibrillation, 57 out of 251 patients with CHB. Although Hanssen (58) found 7 patients with atrial flutter among his 66 with CHB, this combination is regarded as uncommon (101). Diagnostic aspects of atrial fibrillation and complete but also partial heart block have been discussed by Söderström (129).

The *Erlanger-Blackman phenomenon (E B)* is a common arrhythmia in CHB patients. A positive E B implies that the P P intervals with a QRS complex are shorter than those without. It has been presumed that this atrial arrhythmia is due to a baroreceptor reflex with an inhibitory effect on the sinus node induced by each ventricular systole (26). Consequently this arrhythmia may well be influenced by vagolytic or sympathomimetic agents. Excluding the patients who received such agents, it will be found that 38 out of 116 patients (33 %) showed a positive E B (table 7).

Table 8 *Occurrence of arrhythmias and other ECG changes in patients before the onset of complete heart block (CHB) and after CHB had disappeared The figures refer to the number of ECG recordings A V I, A V II and Wenckebach denote first and second degree atrioventricular block and Wenckebach periods respectively RBBB and LBBB denote right and left bundle branch block SES and VES supraventricular and ventricular extrasystoles respectively*

	Sinus	A V I	A V II	Wenckebach	Atrial fibrillation	Atrial flutter
Before CHB	66	31	23	4	17	2
After CHB	52	31	35	11	21	7

	RBBB	LBBB	RBBB + LBBB	Normal QRS duration	Pathological ST T changes	SES	VES
Before CHB	33	15	1	2	49	12	9
After CHB	37	15	1	3	24	3	3

The unknown etiology group displayed a roughly similar distribution (41 %) as did the groups with acute myocardial infarction (26 %) and coronary heart disease (25 %) It was noticeable that no patient in the digitalis intoxication group showed this phenomenon Assuming that the digitalis in these patients causes a pronounced vagal stimulation the further vagal stimulation induced by the baroreceptor reflex secondary to the ventricular systole may be too faint to affect the atrial activity

A reversed E B (i e the P P intervals with a QRS complex are longer than those without) was observed constantly or occasionally in ten cases Three of these had a diagnosis of non acute coronary heart disease and there was an equal distribution between constant and transient CHB A comparison with patients having a positive or no E B showed no characteristic features in survival time (two days to four years mean one and a half year) blood pressure (105/60—220/90, mean 179/79 mm Hg) ventricular rate (34—67 mean 48/min) or atrial rate (62—109 mean 89/min)

For some patients ECG recordings were available *before CHB and after CHB had disappeared* Table 8 shows that A V blocks of the first and second degree as well as bundle branch block especially right sided were common both before CHB and after this had disappeared Wright et al (137) also found a great number of patients with bundle branch block before CHB had been established Penton et al (102) concluded that CHB is frequently preceded by a lesser degree of A V block and is often accompanied or preceded by bundle branch block These authors

Table 6 *Ventricular rate in beats/min in patients with complete heart block*

Ventricular rate beats/min	Unknown etiology	Acute myocardial infarction	Non acute coronary heart disease	Hypertension	Rheum heart disease	Digitalis intoxication	Miscellaneous	Total
0—10	—	—	—	—	—	—	—	—
11—20	1	—	1	—	—	—	—	2
21—30	15	4	1	—	—	1	—	21
31—40	24	19	8	4	2	4	7	68
41—50	20	19	8	7	6	6	8	74
51—60	2	16	3	1	—	2	4	28
61—70	1	2	3	—	1	—	—	7
71—80	1	2	—	—	—	—	—	3
81—90	—	—	—	—	—	1	—	1
Mean	38.3	46.0	44.4	42.7	44.9	47.1	43.6	43.0/204

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	Unknown etiology	Acute myocardial infarction	Non acute coronary heart disease	Hypertension	Rheum heart disease	Digitalis intoxication	Miscellaneous	Total
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Table 9. *Mean values of systolic and diastolic blood pressures and pulse pressure in patients with complete heart block (CHB) at different ventricular rates. Only in 113 patients were both systolic and diastolic blood pressures obtained during CHB*

	Unknown etiology	Acute myocardial infarction	Non-acute coronary heart disease	Hypertension	Rheum. heart disease	Digitalis intoxication	Miscellaneous	Total
Ventricular rate < 40								
Systolic blood pressure	173	157	175	210	195	—	175	175
Diastolic blood pressure	76	62	74	83	50	—	75	74
Pulse pressure	97	95	101	129	145	—	100	100
Number of observations	25	3	7	2	1	—	[illegible]	41
Ventricular rate 40—60								
Systolic blood pressure	191	136	170	230	178	—	174	170
Diastolic blood pressure	[illegible]	70	[illegible]	93	76	—	79	80
Pulse pressure	111	65	95	137	102	—	94	98
Number of observations	25	15	7	6	[illegible]	—	8	60
Ventricular rate > 60								
Systolic blood pressure	200	130	175	—	140	250	—	178
Diastolic blood pressure	70	70	75	—	[illegible]	80	—	62
Pulse pressure	130	60	100	—	140	170	—	11[illegible]
Number of observations	1	1	2	—	1	1	—	6

ond degree were common both before CHB and after CHB had disappeared as were intraventricular disturbances especially right bundle branch block.

F. Blood pressure

The *systolic blood pressure* rose and the *diastolic* pressure fell during CHB compared with the values obtained when the patients did not have any CHB (fig. 6). The resulted in a rise in *pulse pressure* (fig. 6). It will be seen that both the systolic and the pulse pressures rose with age. Also the difference between the pulse pressure in patients with and without CHB tended to increase with age till the eighth decade.

Surprisingly enough there was no correlation between pulse rate and blood pressure in the total material (see table 9). Only the patients with myocardial infarction showed the expected response i.e. decreasing systolic and pulse pressures with increasing ventricular rate. Ide (63) *also found* no significant relationship between wide pulse pressures and slow ventricular rates and a similar conclusion was reached by Ellis (37). Penton et al (102) claimed that greater blood pressure readings are more likely to accompany slower heart rates.

Fatzer (38) stated that young patients with CHB have a normal systolic and diastolic pressure while elderly people have a systolic hypertension

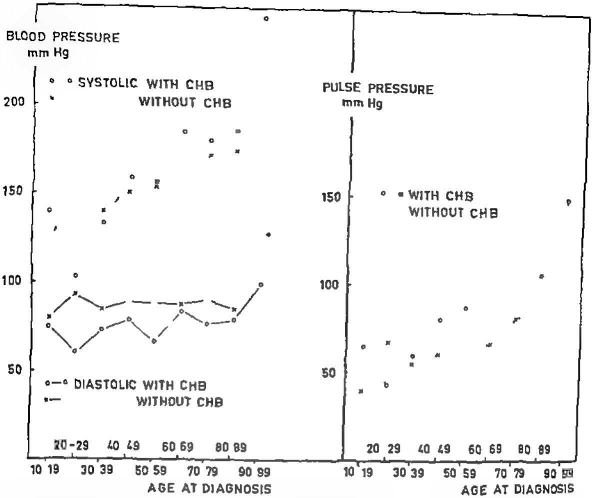

Fig 6 Systolic and diastolic blood pressures and pulse pressure in mm Hg in patients with complete heart block O—O values obtained during CHB x x values obtained before CHB or in the patients with transient CHB after it had disappeared The younger age groups contain only a few number of observations explaining the diverging results in these groups

found first or second degree block or both prior to or subsequent to CHB in 67 patients out of 224 Wyss et al (138) also observed a large number of arrhythmias and bundle branch block before CHB became established

Summarizing the atrial rate which averaged 91 8 beats/min in the total material was higher in the patients with myocardial infarction hypertension and digitalis intoxication The ventricular rate averaged 43 0/min and was higher in patients with myocardial infarction or digitalis intoxication while the unknown etiology group showed lower values Atrial fibrillation was found in 19 and atrial flutter in 2 out of 204 patients A positive Erlanger Blackman phenomenon (E B) was slightly more common in patients with an unknown etiology than in patients with ischemic heart disease A reversed E B was observed in ten cases A V blocks of the first and sec

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Diastolic blood pressure	76	62	74	83	50	—	75	74
Pulse pressure	97	95	101	128	145	—	100	100
Number of observations	25	3	7	2	1	—	3	41
Ventricular rate 40—60								
Systolic blood pressure	191	136	179	230	178	—	174	179
Diastolic blood pressure	[illegible]	70	84	93	76	—	79	80
Pulse pressure	111	65	95	137	102	—	94	98
Number of observations	25	15	7	6	[illegible]	—	8	60
Ventricular rate >60								
Systolic blood pressure	200	130	175	—	140	250	—	178
Diastolic blood pressure	70	70	75	—	0	80	—	[illegible]
Pulse pressure	130	60	100	—	140	170	—	117
Number of observations	1	1	2	—	1	1	—	6

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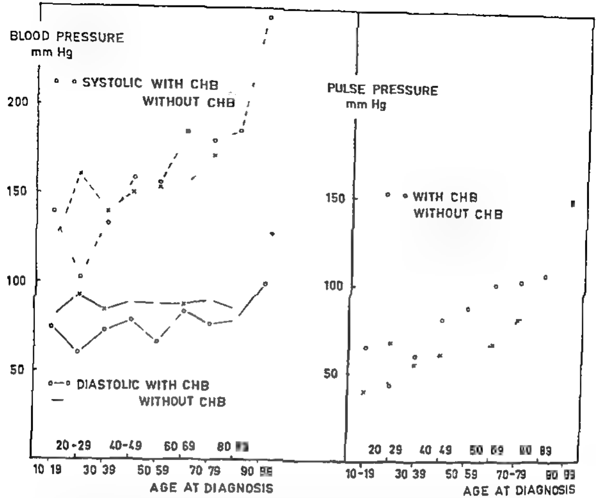

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Prognostic aspects of complete heart block

Major importance was attached to possible prognostic factors in the hope of finding a sign or symptom to aid in the selection of patients with complete heart block (CHB) for pacemaker implantation.

It was apparent that in all groups the highest mortality occurred during the first year after the discovery of CHB. The prognosis study was therefore restricted to this follow-up time. A contributory factor here was the age

Table 10. Total material of 193 patients with complete heart block (CHB) used for the prognostic study. The age groups refer to the age at discovery of CHB. Figures in brackets show the number of women in the group. In age group 85—89 there are thus 1 man and 4 women with unknown etiology

Age	Unknown etiology	Acute myocardial infarction	Non-acute coronary heart disease	Hypertension	Rheum. heart disease	Digitalis intoxication	Miscellaneous	Total
15—19	—	—	—	—	1	—	1 (1)	2 (1)
20—24	1 (1)	—	—	—	—	—	—	1 (1)
25—29	1 (1)	—	—	—	—	1 (1)	—	2 (2)
30—34	—	—	—	—	—	—	1	1
35—39	—	—	—	—	—	—	2 (1)	2 (1)
40—44	1	—	—	—	—	—	2 (1)	3 (1)
45—49	1	3	—	—	1 (1)	—	—	5 (1)
50—54	—	7 (1)	1 (1)	—	3	—	2	13 (2)
55—59	1	5	1	—	—	1	1 (1)	9 (1)
60—64	[illegible] (4)	6 (3)	1	—	—	[illegible]	1	16 (8)
65—69	6 ( )	11 (3)	4 (1)	2 (2)	—	1 (1)	4 (2)	28 (11)
70—74	[illegible] (8)	12 (4)	[illegible]	3 (1)	1	1 (1)	1	35 (14)
75—79	[illegible] (8)	9 (5)	8 (1)	4 (4)	—	3 (2)	3 (1)	44 (17)
80—84	5	4	3 (2)	3 (3)	—	4 (?)	1	19 (6)
85—89	5 (4)	3 (1)	2 (1)	—	—	2 (1)	—	12 (7)
90—94	1	—	—	—	—	—	—	1
Total	59 (24)	60 (17)	23 (5)	12 (10)	6 (1)	14 (9)	19 (7)	193 (73)
Per cent of grand total	30.6 (32.9)	31.1 (23.3)	11.9 (6.8)	6.2 (13.7)	3.1 (1.4)	7.3 (12.3)	9.8 (9.6)	100.0 (100.0)

[illegible]

and an increased pulse pressure Similar results were published by Ellis (37) and Ide (63) *This concept is supported by the findings in the present material* Dividing the patients into two age groups, i e younger than 50 years and 50 years or older, shows that in patients with a pulse rate of 40 beats/min or more, the mean pulse pressure in the younger group is 79 mm Hg (range 45—145 mm Hg) while in the older group it is 106 mm Hg (range 45—200 mm Hg) *This difference is probably significant* ($0.05 > P > 0.01$) An insufficient number of observations was available for patients with a pulse rate of less than 40 beats/min This agrees well with Campbell's (23) argument that the slow forceful heart beat with its long diastole may in some cases contribute to the increase in pulse pressure, though a more important factor is probably the atherosclerosis of the aorta, which diminishes the elasticity and produces a rise in systolic pressure and pulse pressure

Summarizing, CHB was accompanied by an increase in systolic blood pressure and pulse pressure, while the diastolic pressure decreased There was *no correlation between pulse rate and* blood pressure in the total material while the pulse pressure was higher in patients aged 50 years or older compared with patients younger than 50 years

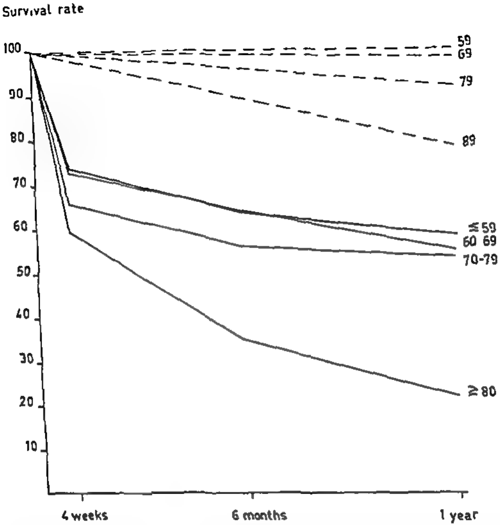

Fig [illegible] Survivorship curves in different age groups —— patients with complete heart block in the present material - - - population of the whole country Survival rate is given in %

improving the prognosis The prognostic study is based on the material presented in table 10 A comparison with table 1 shows that the comparatively largest number of patients have been excluded from the groups with rheumatic heart disease and unknown etiology indicating that the long term prognosis is more favorable in these groups than in the others The sex and age distributions are similar

A Mortality

Table 11 which shows the cumulative number of deaths demonstrates that

Table 11 *Number of deaths in the prognostic study 4 weeks, 6 months and 1 year after the diagnosis of complete heart block in different age groups and classified according to diagnosis*

Age in years at diagnosis	Total material: No of patients dead within 4 weeks	6 months	1 year	Alive after 1 year	Total	Unknown etiology: No of patients dead within 4 weeks	6 months	1 year	Alive after 1 year	Total
≤59	10	14	16	21	37	1	2	2	3	5
60—69	12	16	20	25	45	1	1	2	11	13
70—79	27	34	36	43	79	6	9	10	22	32
≥80	13	21	25	7	32	2	5	8	1	9
Total	62	85	97	96	193	10	17	22	37	59
	Acute myocardial infarction					Nonacute coronary heart disease				
≤59	8	8	9	6	15	0	0	1	1	2
60—69	6	9	10	7	17	3	3	4	1	5
70—79	15	16	16	5	21	1	2	3	7	10
≥80	5	5	5	2	7	5	5	5	1	6
Total	34	38	40	20	60	9	10	13	10	23
	Hypertension					Rheumatic heart disease				
≤59	—	—	—	—	—	1	1	1	4	5
60—69	1	2	2	0	2	—	—	—	—	—
70—79	1	1	1	6	7	0	0	0	1	1
≥80	1	2	2	1	3	—	—	—	—	—
Total	3	5	5	7	12	1	1	1	5	6
	Digitalis intoxication					Miscellaneous				
≤59	0	2	2	0	2	0	1	1	7	8
60—69	0	0	1	1	2	1	1	1	5	6
70—79	2	3	3	1	4	2	3	3	1	4
≥80	0	3	4	2	6	0	1	1	0	1
Total	2	8	10	4	14	3	6	6	13	19

range in the material (from 15 to 91 years), which resulted in too few patients in the different age groups if the follow up time was *not restricted* to one year

It was found that among the original material of 284 patients with CHB extracted *from* the files of the Heart Laboratory there were 11 patients in whom CHB was first diagnosed in *1950* or earlier (*fig 1*) Since there must *have been other* patients from this period who have had CHB but have died these 11 patients represent a positive selection and have therefore been excluded to present them falsely

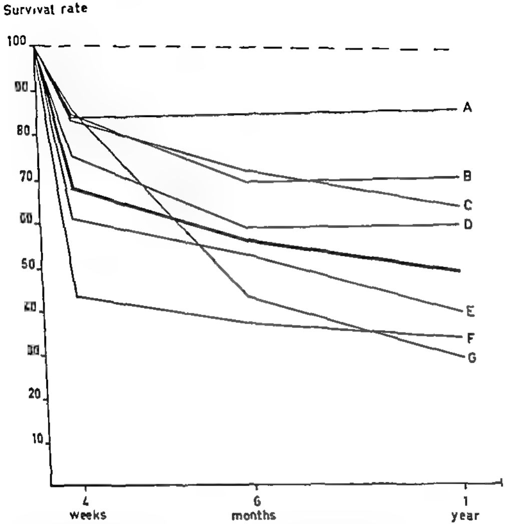

Fig 8. Survival rate at 4 weeks, 6 months and 1 year after the onset of complete heart block

A rheumatic heart disease
B miscellaneous
C unknown etiology
D hypertension
E coronary heart disease
F myocardial infarction
G digitalis intoxication

Heavy line indicates the mean for the total material. Dashed line indicates the 1 year survival rate in the population of the whole country at the mean age of the material. Survival rate is given in %.

Table 12 Excess one year mortality in % in different age groups

Age in years	<59	60—69	70—79	>80
Excess one year mortality in %	41 0	42 4	38 0	56 0

one third of the patients die not more than four weeks after the diagnosis of *CHB* and that one year after the diagnosis only half of the patients are alive The *mortality* figures increase with age so that the one year mortality in patients 80 years old or more is 78 %, compared with 43 % in patients 59 years old or younger The same tendency is found in the 4 week mortality, the corresponding figures being 41 % and 27 %

This higher mortality in the older patients is to some extent caused by the higher age as shown in fig 7 The dashed lines indicate the survivorship curves for the national population of the country The population figures have been taken from the Statistical Abstracts of Sweden (121) and chosen to represent the highest age in each age group—in the youngest age group, for example, the survival figure for the population refers to men and women 59 years old while all the patients with CHB in this group are 59 years or younger The excess mortality expressed as the difference between the mortality in the population and the patients with CHB is given in table 12

Table 11 also gives the material broken down according to the etiology of CHB Fig 8 shows the survivorship curves for the different diagnoses as well as for the total material and the one year survival rate in the total population It was found that the prognosis is worst in patients with *acute myocardial infarction* with 34 out of 60 patients (57 %) dead within 4 weeks and 67 % dead within a year Moreover, the prognosis became worse with increasing age, the 4 week mortality being 53 % in patients 59 years or younger and 71 % in patients in the two highest age groups The prognosis is almost as bad for patients with *non acute coronary heart disease* It is also very unfavorable in patients with *digitalis intoxication* 14 % being dead within 4 weeks but 71 % within one year The explanation for this discrepancy between the 4 week and one year mortalities could be that these patients were in a bad condition and received a high digitalis dosage as a desperate attempt at improvement This overdosage resulted in a CHB and the patient died not of the digitalis overdosage—4 week mortality low—but of the severe heart disease—one year mortality high This is supported by the finding that 13 of the 14 patients in the digitalis intoxication group were classified as transient CHB

The one year mortality in the group with *hypertensive heart disease* was 42 % and 37 % in the group with *unknown etiology* as shown in fig 8 and table 11 In the latter group the 4 week

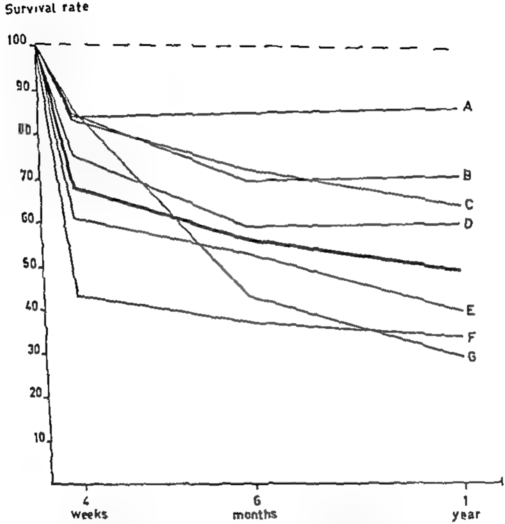

Fig. 8. Survival rate at 4 weeks, 6 months and 1 year after the onset of complete heart block.

A rheumatic heart disease
B miscellaneous
C unknown etiology
D hypertension
E coronary heart disease
F myocardial infarction
G digitalis intoxication

Heavy line indicates the mean for the total material. Dashed line indicates the 1 year survival rate in the population of the whole country at the mean age of the material. Survival rate is given in %.

Table 12 *Excess one year mortality in % in different age groups*

Age in years	⩽59	60—69	70—79	>80
Excess one year mortality in %	41.0	42.4	38.0	56.0

one third of the patients die not more than four weeks after the diagnosis of CHB and that one year after the diagnosis only half of the patients are alive. The *mortality figures increase* with age so that the one year mortality in patients 80 years old or more is 78 %, compared with 43 % in patients 59 years old or younger. The same tendency is found in the 4 week mortality, the corresponding figures being 41 % and 27 %.

This higher mortality in the older patients is to some extent caused by the higher age as shown in fig 7. The dashed lines indicate the survivorship curves for the national population of the country. The population figures have been taken from the Statistical Abstracts of Sweden (121) and chosen to represent the highest age in each age group—in the youngest age group for example, the survival figure for the population refers to men and women 59 years old while all the patients with CHB in this group are 59 years or younger. The excess mortality expressed as the difference between the mortality in the population and the patients with CHB is given in table 12.

Table 11 also gives the material broken down according to the etiology of CHB. Fig 8 shows the survivorship curves for the different diagnoses as well as for the total material and the one year survival rate in the total population. It was found that the prognosis is worst in patients with *acute myocardial infarction* with 34 out of 60 patients (57 %) dead within 4 weeks and 67 % dead within a year. Moreover, the prognosis became worse with increasing age, the 4 week mortality being 53 % in patients 59 years or younger and 71 % in patients in the two highest age groups. The prognosis is almost as bad for patients with *non acute coronary heart disease*. It is also very unfavorable in patients with *digitalis intoxication*, 14 % being dead within 4 weeks but 71 % within one year. The explanation for this discrepancy between the 4 week and one year mortalities could be that these patients were in a bad condition and received a high digitalis dosage as a desperate attempt at improvement. This overdosage resulted in a CHB and the patient died not of the digitalis overdosage—4 week mortality low—but of the severe heart disease—one year mortality high. This is supported by the finding that 13 of the 14 patients in the digitalis intoxication group were classified as transient CHB.

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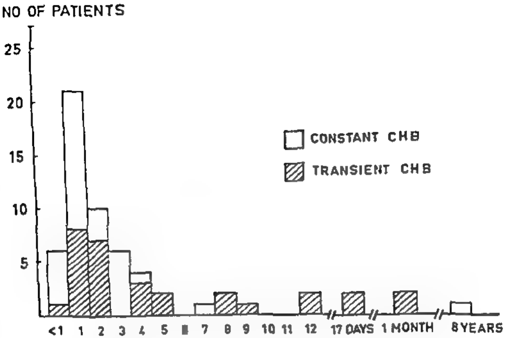

Fig. 9. Duration of complete heart block (CHB) in patients with acute myocardial infarction. The patients with transient CHB have all survived while all patients with constant CHB have died except one being still alive at the follow up examination 8 years after the infarction.

an acute myocardial infarction is very rare.

The *location of the myocardial infarct* was usually *posterior* (68 %). In 22 % the infarct was anterior and in 10 % a combined anterior and posterior infarct was found. The predominance of the posterior location reflects the anatomy of the blood supply, since the A V node and the common truncus *of the bundle of His* usually receive their blood from the right coronary artery as discussed for instance by Reuders (103) and Lev (86). These anatomical characteristics may well explain the high mortality in CHB patients with an anteriorly situated infarct (table 13). A patient who develops CHB in connection with an anterior infarction probably has a highly deteriorated right coronary circulation and collaterals to the A V node have developed from the left coronary artery. An occlusion of the left coronary artery system will then have a fatal effect on the myocardial circulation.

The *cause of death* in these patients with CHB is shown in table 14 from which it will be seen that the CHB including Adams Stokes attacks caused death in one third of the cases. It was sometimes difficult to determine the cause of death from the patient records which is why only 141 patients are

mortality was less than half that after one year, which is the reverse of the pattern for the myocardial infarction group

The *rheumatic heart disease* group had a strikingly low mortality (fig 8) This is also evident from the fact that the biggest difference in the number of patients between table 1 and table 10 was found in this group The figures on the cumulative number of deaths given for the *miscellaneous group* in table 11 are very similar to those in the group with unknown etiology

An advantage of the Malmo material is that it contains most of the patients known to have CHB in a defined population Many of the materials published are selected, and detailed prognostic studies separating patients with CHB of different etiology are rather sparse The overall mortality varies in different materials Wilhus (136) was able to trace 22 of his 37 patients with CHB Of these 68 % had died from heart disease an average of seven months after examination Usually the reported survival figures seem to be better than in the Malmo material, although they are not always comparable Graybiel and White (53) observed an average survival time of 1 year and 7 *months in 30 patients* dying of cardiovascular disease In Campbell's (23) material 34 patients out of 50 followed for more than 2 years or until their death had died after an average of 2 5 years and Wright et al (137) calculated that the average life expectancy is generally 3—4 years

Graybiel and White (53) stressed the necessity of distinguishing between CHBs of different etiology Penton et al (102) found the average survival time after the first appearance of CHB to be 26 2 months In the *rheumatic* heart disease group it was 38 4 months which agrees with the comparatively favorable prognosis in the Malmö material Curd et al (31), on the other hand observed a *high mortality in* their patients with valvular heart disease and CHB, but many of these were functionally in a very bad condition

Most authors agree that CHB produced by *myocardial infarction* has the worst prognosis (31, 102 106) which tallies with the present results CHB usually develops very soon after the myocardial infarction In the present material the *interval between the myocardial infarction and CHB* was 24 hours or less in 53 %, while 84 % had developed CHB within three days The duration of CHB was usually short as shown in fig 9 In the patient in fig 9 who survived eight years no preinfarction ECG was recorded but a *blood pressure of 140/100* had been measured half a year before the infarction

There was then only one case in this material in which CHB, probably produced by a myocardial infarction persisted for a long time Penton et al (102) also found only one such patient Rowe and White (106) had seven patients out of 38 in whom CHB persisted for more than one month after the myocardial infarction and in two CHB lasted for three years It may be concluded that persistent CHB after

al (102) the cause of death was known in 89 out of 127 patients Sudden death occurred in 39 while 22 died of acute coronary occlusion 10 of progressive heart failure and 18 of miscellaneous causes In his material comprising other types of A V block as well as CHB Campbell (23) reported 24 patients with Adams Stokes attacks 14 of whom died suddenly Of the 10 patients without Adams Stokes attacks only one died suddenly and four of cardiac decompensation Campbell (23) remarked that patients with or without previous heart block may sometimes die in their first Adams Stokes attack and so come under the pathologist rather than the clinician but judging from his own material he thinks this occurs only rarely

Summarizing 193 patients with CHB first diagnosed during 1951—1964 have been analyzed As shown in fig 8 half of the patients in the total material died not more than a year after diagnosis The highest mortality was found in patients with myocardial infarction especially when this was situated anteriorly and the lowest in patients with rheumatic heart disease The interval between the myocardial infarction and the appearance of CHB was usually short 81 % had developed CHB within three days Persistent CHB *after* a myocardial infarction is very uncommon with just one possible case in the *present material*

B Clinical factors

One might expect the occurrence of Adams Stokes attacks to impair the prognosis in patients with CHB However a review of the literature reveals that this is not always so Rowe and White (106) found to their surprise that patients with Adams Stokes attacks survived more than twice as long from onset as those without Meyer Leddin (97) concluded that there is no immediate correlation between the survival time and the frequency of Adams Stokes attacks Similarly Curd et al (31) observed that survival did not differ much in relation to the presence or absence of Adams Stokes attacks This agrees with the observation that some patients can survive many years after the first Adams Stokes attack (65) On the other hand Ellis (37) concluded that Adams Stokes attacks often have a serious prognosis and Campbell (23) analyzing a material of 64 cases of heart block mostly complete found that the prognosis was considerably worse when Adams Stokes attacks supervened Hanssen (58) reported that among 12 patients dying during the first observation year 11 had suffered from Adams Stokes attacks

In the Malmö material presented in table 15 the one year survival rate was 50 out of 111 patients with *syncope* (45 %) as against 46 out of 79 without syncope (58 %) The difference was especially pronounced among patients with myocardial infarction and non acute coronary heart disease but also for the miscellaneous group although the figures in this group are smaller It is remarkable that for the patients *with unknown etiology* the proportion between those with and without syn

Table 13 *Number of deaths in patients with complete heart block as a complication to an acute myocardial infarction, situated anteriorly, posteriorly or both Figures in brackets mean % of grand total*

Location of infarct	No of patients dead within			Alive after 1 year	Total (%)
	4 weeks	6 months	1 year		
Posterior	20	23	25	16	41 (68)
Anterior	*11*	*12*	*12*	*1*	*13 (22)*
Posterior and anterior	3	3	3	3	6 (10)

Table 14 *Cause of death in the 141 patients with complete heart block (CHB) in the prognostic study in whom the mode of death was known*

	CHB including Adams Stokes attacks	Cardiac disease other than CHB	Noncardiac disease
Unknown etiology	19	7	16
Acute myocardial infarction	13	35	2
Nonacute coronary heart disease	7	8	2
Hypertension	2	8	1
Rheumatic heart disease	1	1	—
Digitalis intoxication	—	5	6
Miscellaneous	5	2	1
Total	47	66	28
% of grand total	33	47	20

listed in the table Moreover, the figure 13 for the myocardial infarction group is probably too low because only those patients were included in whom there was no doubt that the CHB including Adams Stokes attacks caused death The type of arrhythmia during the Adams Stokes attack in these 13 patients is not known Had it been a bradyarrhythmia artificial pacing might have been of value This is supported by the fact that Bruce et al (19) found an overall mortality of 11 % in patients with bradyarrhythmias including CHB complicating an acute myocardial infarction when they were treated promptly with catheter pacing However Cosby et al (30) observed no improvement in mortality figures in the presence of acute myocardial infarction—60 % before pacing and 62 % in 17 paced patients Gurd et al (31) are also pessimistic on this point

The mode of death in patients with CHB is not often discussed in the literature Graybiel and White (53) reported 11 cases of sudden death including Adams Stokes attacks in 30 cases dying of cardiovascular disease In the material reported by Penton et

al (102) the cause of death was known in 89 out of 127 patients. Sudden death occurred in 39, while 22 died of acute coronary occlusion, 10 of progressive heart failure and 18 of miscellaneous causes. In his material comprising other types of A-V block as well as CHB, Campbell (23) reported 24 pa-tients with Adams-Stokes attacks, 14 of whom died suddenly. Of the 10 pa-tients without Adams-Stokes attacks only one died suddenly and four of cardiac decompensation. Campbell (23) remarked that patients with or with-out previous heart block may some-times die in their first Adams-Stokes attack and so come under the pathol-ogist rather than the clinician, but judging from his own material he thinks this occurs only rarely.

Summarizing, 193 patients with CHB first diagnosed during 1951—1964 have been analyzed. As shown in fig 8 half of the patients in the total material died not more than a year after diag-nosis. The highest mortality was found in patients with myocardial infarction, especially when this was situated an-teriorly, and the lowest in patients with rheumatic heart disease. The in-terval between the myocardial infarc-tion and the appearance of CHB was usually short: 84 % had developed CHB within three days. Persistent CHB after a myocardial infarction is very uncommon, with just one pos-sible case in the present material.

B. Clinical factors

One might expect the occurrence of Adams-Stokes attacks *to impair the* prognosis in patients with CHB. How-ever, a review of the literature reveals that this is not always so. Rowe and White (106) found to their surprise that patients with Adams-Stokes at-tacks survived more than twice as long from onset as those without. Meyer-Leddin (97) concluded that there is no immediate correlation between the survival time and the frequency of Adams-Stokes attacks. Similarly Curd et al (31) observed that survival did not differ much in relation to the pres-ence or absence of Adams-Stokes at-tacks. This agrees with the observa-tion that some patients can survive many years after the first Adams-Stokes attack (65). On the other hand Ellis (37) concluded that Adams-Stokes attacks often have a serious prognosis, and Campbell (23), analyzing a material of 64 cases of heart block, mostly complete, found that the prog-nosis was considerably worse when Adams-Stokes attacks supervened. Hanssen (58) reported that among 12 patients dying during the first obser-vation year 11 had suffered from Adams-Stokes attacks.

In the Malmö material presented in table 15 the one year survival rate was 50 out of 111 patients with *syncope* (45 %) as against 46 out of 79 without syncope (58 %). The difference was especially pronounced among patients with myocardial infarction and non-acute coronary heart disease but also for the miscellaneous group, although the figures in this group are smaller. It is remarkable that for the patients with unknown etiology the proportion between those with and without syn-

Table 15 *Number of patients with complete heart block classified according to 1 year survival, having syncope and verified Adams Stokes attacks, respectively* ? = *no reliable information available on the occurrence of syncope or Adams Stokes attacks*

Diagnosis	Syncope						Adams Stokes attacks					
	Alive after 1 year			Dead within 1 year			Alive after 1 year			Dead within 1 year		
	Yes	No	?	Yes	No	?	Yes	No	?	Yes	No	?
Unknown etiology	30	7	—	16	4	2	14	17	6	10	[illegible]	6
Acute myocardial infarction	4	16	—	28	12	—	2	[illegible]	16	11	16	13
Nonacute coronary heart disease	3	7	—	9	4	—	—	3	7	7	2	4
Hypertension	4	3	—	2	3	—	1	3	3	1	1	3
Rheumatic heart disease	2	3	—	—	1	—	1	1	3	—	—	1
Digitalis intoxication	3	1	—	3	7	—	1	2	1	—	3	7
Miscellaneous	4	0	—	3	2	1	2	2	9	3	—	3
Total	50	46	—	61	33	3	21	30	45	32	28	37
% of total	26	24	—	32	17	1	11	16	23	17	14	19

copal attacks was 4 1 both among the patients alive after one year and among those dead within one year

A further analysis of table 15 shows the result for the one year follow up in relation to patients in whom the diagnosis of *Adams-Stokes attack* was beyond doubt, i e in whom the pulse was palpated or an ECG recorded during the attack (65) For this group the one year survival was lower than for the rest of the material, although the difference was not striking It is noticeable that in patients with unknown etiology there was a tendency to a *worse prognosis* when CHB was complicated with Adams Stokes attacks However none of these differences were statistically significant ($P > 0.1$)

To sum up, the occurrence of syncope or Adams Stokes attacks in patients with CHB seemed to make the one year survival rate more unfavorable but the differences were not striking

C Electrocardiographic factors

Several parameters in the electrocardiogram (ECG) were analyzed in the hope of finding something of prognostic significance *The atrial rate* was slightly higher in patients dead within one year compared with patients alive after one year This tendency was less pronounced in the myocardial infarction group as shown in table 16 However none of the observed differences were statistically significant ($P > 0.05$) Fig 10 illustrates in more detail the prognostic significance of the atrial rate in the total material

The difference in *ventricular rate* between patients alive and dead within one year was very small (table 16) and in the three largest groups there was rather a tendency to lower rate in those dead within one year. The differences observed were not statistically significant except in the digitalis intoxication group (0.05>P>0.01). The follow up is illustrated in more detail in fig 11. The pulse rate in CHB displays some variations though the degree of spontaneous variation was of no prognostic value. The means of the *quotient between the atrial and ventricular rates* are given in table 16 and show little difference between patients dead and alive after one year respectively.

Ellis (37) was not able to find any correlation between pulse rate and mortality. Cosby et al (30) studied atrial rate, ventricular rate, degree of variation of both atrial and ventricular rate, presence or absence of changing block, and width of the QRS in 100 unselected patients with CHB but found no significant correlations to clinical status or prognosis.

Among the patients showing a positive *Erlanger Blackman phenomenon*[*] (E B) the ratio between those alive and dead respectively after one year was 2:1 while in patients not showing E B it was 1:1 which *indicates that a positive E B is favorable* (table 17). The difference was however not significant (P>0.1).

The E B can be quantified by calculating the *quotient between the longest and shortest P P interval*. It was found that a high E B quotient cannot be said to be of prognostic significance in individual cases.

An abnormally prolonged QRS (≥0.12 secs) in combination with CHB may appear not only in true bundle branch block but also when the pacemaker is situated far distally from the A V node and there is no bundle branch block, as well as in bilateral bundle branch block lesions. Since it is often difficult to differentiate between these etiologies the term *bundle branch block type* is used here when the QRS is abnormally prolonged in patients with CHB.

Various incidences are reported for this abnormality in patients with CHB but it is usually found in about half (63, 74, 97, 102, 136). The findings in the largest groups of the Malmö material are presented in fig 12. Bundle branch block type did not seem to imply a worsened prognosis in the group with unknown etiology while the high mortality in the patients with myocardial infarction was further increased by this complication. In the coronary heart disease group, too, the prognosis was most favorable when the QRS duration was within the normal range. There did not seem to be any prognostic difference between left and right bundle branch block type. It is remarkable how often right and left bundle branch block type or both these patterns alternately (*group III in fig 12*) were found in the group with unknown etiology, differing in this respect from patients with nonacute cor

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[*] See page 28 for explanation

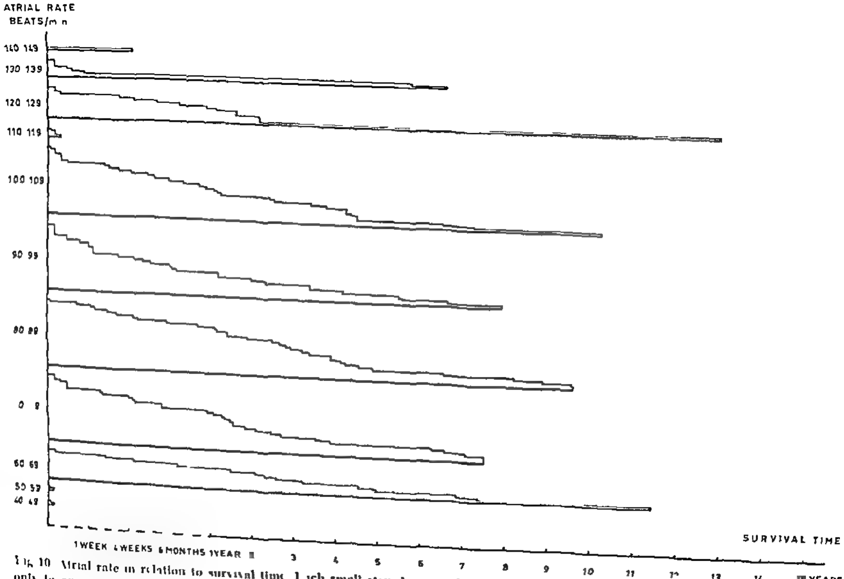

Fig. 10 Atrial rate in relation to survival time. Each small step downwards indicates death of one patient. Survival time is not restricted only to one year. Patients with atrial fibrillation and atrial flutter are excluded.

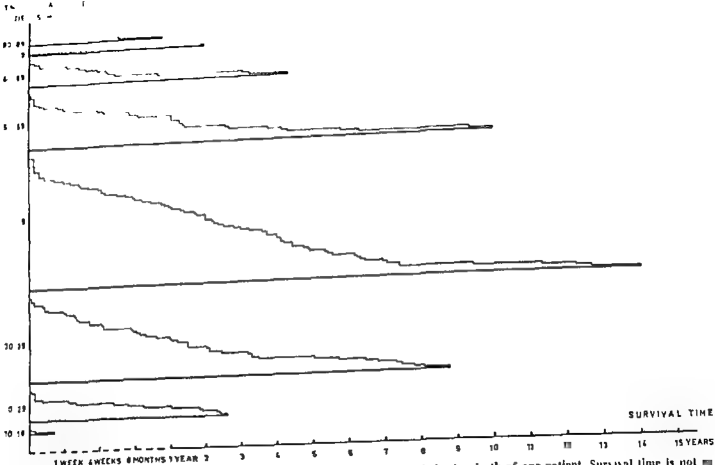

Fig 11 Ventricular rate in relation to survival time Each small step downwards indicates death of one patient Survival time is not restricted only to one year

Table 16 *Atrial rate and ventricular rate in beats/min and quotient atrial rate/ventricular rate in patients with complete heart block (CHB), classified according to 1 year survival. Twenty one patients with atrial fibrillation or atrial flutter were excluded from the atrial rate and quotient groups*

Diagnosis	Atrial rate in beats/min during CHB				Ventricular rate in beats/min during CHB				Quotient atrial rate/ventricular rate during CHB			
	Alive after 1 year		Dead within 1 year		Alive after 1 year		Dead within 1 year		Alive after 1 year		Dead within 1 year	
	Mean	No of patients	Mean	No of patients	Mean	No of patients	Mean	No of patients	Mean	No of patients	Mean	No of patients
Unknown etiology	97	35	94	22	39	37	37	22	2.3	35	2.8	22
Acute myocardial infarction	94	20	90	38	49	20	45	40	2.0	20	2.2	38
Nonacute coronary heart disease	84	7	94	11	45	10	41	13	1.8	7	2.5	11
Hypertension	93	5	100	4	41	7	45	5	2.2	5	2.2	4
Rheumatic heart disease	95	4	86	1	45	5	67	1	2.1	4	1.3	1
Digitalis intoxication	97	2	94	6	42	4	49	10	2.0	2	1.7	6
Miscellaneous	81	11	94	6	43	13	46	6	2.0	11	2.2	6
Total	89	84	[illegible]	88	43	96	44	97	2.1	84	2.3	88

Table 17 *Occurrence of a positive Erlanger Blackman phenomenon in patients with complete heart block classified according to 1 year survival. Only the 108 patients in the prognostic study not treated with vagolytic or sympathomimetic agents are included*

	Unknown etiology		Acute myocardial infarction		Nonacute coronary heart disease		Hypertension		Rheumatic heart disease		Digitalis intoxication		Miscellaneous		Total	
	Alive after 1 year	Dead within 1 year	Alive after 1 year	Dead within 1 year	Alive after 1 year	Dead within 1 year	Alive after 1 year	Dead within 1 year	Alive after 1 year	Dead within 1 year	Alive after 1 year	Dead within 1 year	Alive after 1 year	Dead within 1 year	Alive after 1 year	Dead within 1 year
E B	12	5	3	5	1	2	1	—	2	—	—	—	5	—	21	12
No E B	13	7	7	15	4	[illegible]	3	1	1	1	2	[illegible]	4	4	34	38

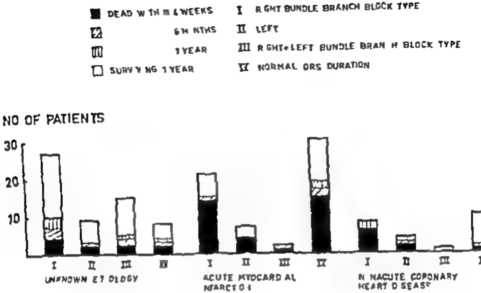

Fig. 12. Bundle branch block type in relation to survival time in the three largest groups

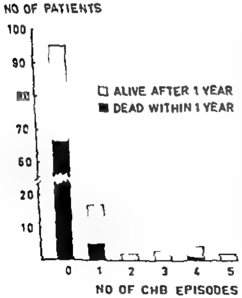

Fig. 13. Number of episodes of complete heart block (CHB) in patients with constant CHB. No episodes means that CHB was recorded in all ECGs

onary heart disease and acute myocardial infarction.

The *number of episodes of CHB* in relation to the one year survival rate is shown in fig. 13. The one year mortality was not increased with an increasing number of CHB episodes, nor was there any correlation between the duration of the CHB episodes and the one year mortality. It is often said that patients who repeatedly change between different rhythms have a worse prognosis and are therefore regarded as candidates for artificial pacing to a greater extent than are patients with a constant CHB. Apparently this is not always so.

This problem can also be illustrated by a comparison of the one year mortality in patients with constant and transient CHB. Excluding patients with CHB episodes before the permanent

CHB was established it was found that 28 patients (30 %) with a constant CHB survived one year while 66 (70 %) had died within this time interval The corresponding figures for patients with transient CHB were 45 (64 %) and 25 (36 %) This difference is highly significant ($P<0\ 001$) A number of patients with constant CHB showed some episodes of CHB before the permanent CHB appeared In this group, which is more similar to the transient group from the rhythm change aspect, 23 patients (79 %) survived one year while 6 (21 %) did not If compared with constant CHBs without CHB episodes this difference is also highly significant ($P<0\ 001$)

Similar results have been reported by Campbell (23), who noted that changes of rhythm did not seem to affect the prognosis unless they were associated with Adams Stokes attacks and Zion and Bradlow (142) observed in their material a mortality of 66 % at follow up in the patients with permanent block and 25 % in the patients with intermittent or temporary block

Summarizing, several electrocardiographic features have been analyzed from a prognostic point of view The atrial rate was usually slightly higher in patients surviving less than one year compared with those surviving one year or more while the difference in ventricular rate was smaller The quotient between the atrial and ventricular rates was of no prognostic value A positive Erlanger Blackman phenomenon seemed to be favorable but the degree of benefit could not be quantified by calculating the quotient between the longest and shortest P P intervals Although bundle branch block type was often found among patients with unknown etiology it did not seem to imply a poorer prognosis in this group in contrast to the findings in patients with acute myocardial infarction and coronary heart disease The one year survival rate was not influenced by the number of episodes of CHB Constant CHB implied a lower one year survival rate than transient CHB

D Blood pressure and X-ray findings

The prognostic significance of the blood pressure was studied The *systolic blood pressure* averaged 185 mm Hg in patients alive after one year while it was 173 mm Hg in patients dead within one year This difference is not significant ($P>0\ 05$) The *diastolic blood pressure* showed less pronounced changes with means in the total material of 79 and 76 mm Hg respectively It follows that the *pulse pressure* was higher in the one year survivors than in those dead within one year In spite of these differences between the averages the prognosis could not be predicted accurately for individual cases

The *roentgenological heart volume* calculated as ml per square meter body surface area could not be used to predict the prognosis as is apparent from a detailed analysis of fig 14 Only in the nonacute coronary heart disease group was there a tendency to a higher one year mortality among patients

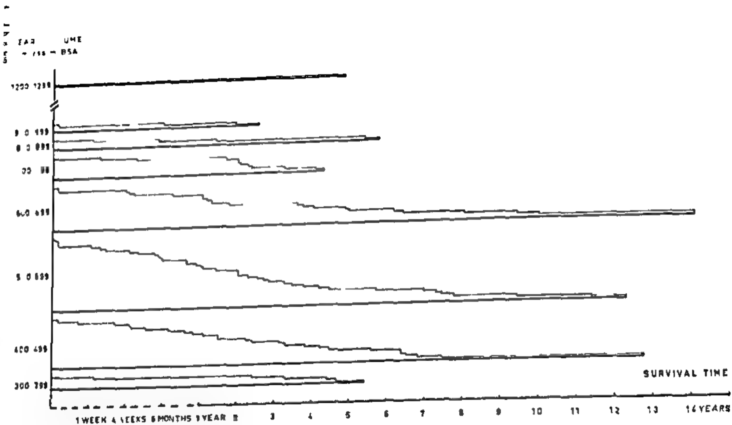

Fig. 14 Heart volume in ml/sq m BSA in relation to survival time. See legend fig. 11

CHB was established it was found that 28 patients (30 %) with a constant CHB survived one year while 66 (70 %) had died within this time interval. The *corresponding figures for* patients with transient CHB were 45 *(64 %)* and 25 *(36 %)*. This difference is highly significant ($P<0.001$). A number of patients with constant CHB showed some episodes of CHB before the permanent CHB appeared. In this group, which is more similar to the transient group from the rhythm *change aspect*, 23 patients *(79 %)* survived one year while 6 (21 %) did not. If compared with constant CHBs without CHB episodes this difference is also highly significant ($P<0.001$).

Similar results have been reported by Campbell (23), who noted that changes of *rhythm did not seem to* affect the prognosis unless they were *associated with Adams Stokes attacks* and Zion and Bradlow (142) observed in their *material* a mortality of 66 % at follow up in the patients with permanent block and 25 % in the patients with intermittent or temporary block.

Summarizing, several electrocardiographic features have been analyzed *from* a prognostic point of view. The atrial rate was usually slightly higher in patients surviving *less than one year* compared with those surviving one year or more while the *difference in* ventricular rate was smaller. The quotient between the atrial and ventricular rates was of no prognostic value. A positive Erlanger Blackman phenomenon seemed to be favorable but the degree of benefit could not be quantified by calculating the quotient between the longest and shortest P P intervals. *Although bundle branch block* type was often found among patients *with unknown etiology* it did not seem to imply a poorer prognosis in this group in contrast to the findings in patients with acute myocardial infarction and coronary heart disease. The one year survival rate was not influenced by the number of episodes of CHB. *Constant CHB implied a lower one* year survival rate than transient CHB.

D. Blood pressure and X-ray findings

The prognostic significance of the blood pressure was studied. The *systolic blood pressure* averaged 185 mm Hg in patients alive after one year while it was 173 mm Hg in patients *dead within one year*. *This difference* is not significant ($P>0.05$). The *diastolic blood pressure* showed less pronounced changes with means in the total material of 79 and 76 mm Hg respectively. It follows that the *pulse pressure* was higher in the one year survivors than in those dead within one year. In spite of these differences between the averages the prognosis could not be predicted accurately for *individual cases*.

The *roentgenological heart volume calculated* as ml per square meter body surface area could not be used to predict the prognosis as is *apparent from* a detailed analysis of fig 14. Only in the nonacute *coronary heart disease* group was there a tendency to a higher one year mortality among patients

Material and methods. Hemodynamic study

A. Material

Although many of the living patients were in an unsatisfactory condition occasioned by various diseases, there were 20 who could be subjected to further hemodynamic studies (fig. 1). Twelve of these had complete heart block (CHB) at examination. As this group was rather small, 7 patients with CHB from other hospitals outside Malmö were added. The total number of CHB patients subjected to hemodynamic and pharmacologic studies was then 27, of whom 19 had a *CHB at examination (group B)*. Eight patients had had a transient CHB in connection with a previous acute disease. These patients constitute the *reference material with sinus rhythm at examination (group T)*. Clinical data are given in the Appendix, table A. The results of these studies are presented in chapters VI, VII and VIII.

B. Methods

All catheterization studies were performed by myself. The patients arrived for the examination in the morning after a light breakfast. No premedication was given. Any therapy was not withdrawn before the examination.

The catheters were inserted with Seldinger technique (113) under local anesthesia with 2 % Xylocaine (Astra®). A 27 cm long polyethylene catheter PE 160[1] was introduced about 20 cm into the right brachial artery. A teflon catheter[2], 100 cm long and of a size to fit the PE 160, with a flexible stainless steel wire guide, was introduced with the aid of fluoroscopy through the left brachial artery into the middle part of the ascending aorta. The tip of a venous catheter, either a 100 cm long PE 160 catheter with a flexible stainless steel wire guide inserted percutaneously or a single lumen Cournand catheter number 8[3], was manipulated under fluoroscopical control into the middle of the right atrium.

Cardiac output (CO) was determined by dye dilution technique according to Hamilton et al. (57). Three ml of a 5 % sodium bromsulphalein solution (131) was rapidly injected into the right atrium and the catheter was immediately flushed with saline. The same batch of bromsulphalein was

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[1] Clay Adams, New York.
[2] Manufactured by Stille, Stockholm.
[3] United States Catheters and Instrument Corp., Glens Falls, N.Y., USA.

with big hearts, but there were many exceptions

To *sum up*, systolic blood pressure and pulse pressure were higher among the one-year survivors than among patients dead within a year in the total material. The prognosis in individual cases could not be predicted accurately from the blood pressure values or the X-ray findings.

tained by entering a DuBois nomogram.

The systemic *vascular resistance* expressed in dyn sec cm⁻⁵ was calculated as the difference between the mean aortic and mean right atrial pressures in mm Hg, divided by the cardiac output in ml/sec and multiplied by 1332 (2).

Arterial lactate concentration was determined enzymatically according to a slight modification of the method of Hohorst (60).

Serum creatinine was measured with a Technicon Auto Analyzer[1], using a modification of the Folin and Wu method (77). Creatinine *clearance* was calculated using a four hour interval for the collection of urine. The urine creatinine was determined with the Jaffe method (77).

C. Catheterization procedure

Once the catheter had been introduced the patients were allowed to rest for half an hour. CO, pressure recordings and ECG were obtained 30 and 40 minutes after introduction of the catheters. The patient was then tilted for the *orthostatic test* to an angle of 53° to the horisontal plane. The pressure recording apparatus was adjusted to the phlebostatic level (107). Pressures and ECG were recorded each minute and CO was done 1, 3 and 10 minutes after tilting the patient. After 10 minutes the patient was tilted back to the horizontal position and pressures and ECG were recorded each minute for 4 minutes.

After 5—10 minutes rest the patient was prepared for the *exercise test*. During collection of expired air in a Douglas bag for determination of oxygen consumption a new CO determination was done, as were ECG and pressure recordings in the right atrium and aorta. An arterial sample was drawn for determination of lactate concentration, pH, PaO_2, $PaCO_2$ and standard bicarbonate. The patient was then exercised for 8 minutes, if possible, in the supine position on a bicycle ergometer. The load varied but was usually 300 kpm/min for men and 200 kpm/min for women (individual values are given in the Appendix, table C). From the values obtained at the previous exercise described in chapter II the load during catheterization was calculated to be maximal.

CO was determined after 1, 4 and 8 minutes exercise as well as 4, 10 and 30 minutes after the end of exercise. *Pressures and ECG* were recorded every minute during exercise and for 4 minutes afterwards and at 8, 8, 10, 15, 20 and 30 minutes after the end of exercise. *Expired air* was collected during the last 3 minutes of exercise and during the 2nd to 6th and 8th to 12th minutes after the end of exercise. *Arterial samples* for determination of *pH, PaO_2, $PaCO_2$* and standard bicarbonate were drawn at the *end of* and *10 minutes after exercise*. Blood for lactate concentration was drawn *after* 4 and 8 minutes exercise and 4, 10, 20 and 30 minutes after exercise.

Mingograph 4, Elema-Schönander, Stockholm, Sweden.

[1] Technicon Instruments Corp., Chauncey, N.Y., USA.

used for the entire study. The blood was *collected through the right brachial artery catheter in heparinized tubes moved automatically so that one blood* sample was obtained every second. Only in a few cases was *the flow* so slow that the samples were obtained every other second. In some determinations the linear portion of the disappearance slope could not be identified on the semilogarithmic scale. In these cases the forward triangle method according to Hetzel et al. (59) was used. These values are marked with an asterisk in the tables in the Appendix.

Hematocrit was determined in duplicate on arterial blood drawn into an Ellermann tube. After thorough mixing, a 75 mm heparinized microhematocrit tube was filled and centrifuged at 8 000 r.p.m. for at least 5 minutes. Hematocrit was measured after each CO determination. The *mean transit time* (MTT) was calculated according to Hamilton et al. (57) and the *central blood volume* (CBV) as MTT (sec) × CO (ml/sec).

Expired air was collected in a Douglas bag for 5—7 minutes after an initial 2 minute adaptation period. After collection for 2 ½—3 ½ minutes, an arterial blood sample was drawn for determination of pH, arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$) and standard bicarbonate. pH was measured with a conventional technique (*normal range in* arterial blood 7.35—7.45). *PaO_2* was measured with a *modified Clark* electrode (28), normal range 83—104 mm Hg, and *$PaCO_2$* according to Severinghaus and Bradley (115). Normal range 34—43 mm Hg. *Standard bicarbonate* was determined according to Jorgensen and Astrup (70) with a normal range of 19—24 mEq/l. Expired air collected *in Douglas bags* was analyzed in triplicate with a Scholander gas analysis apparatus* in order to obtain the amount of *oxygen consumed* per minute. The *arterio venous oxygen difference*, (a-v)O_2 difference, was calculated from the Fick equation.

Pressure curves from the right atrium and ascending aorta were obtained with a four channel direct writing ink jet electrocardiograph*. Mean pressures were obtained by electrical integration over a period including at least two respiratory cycles. Zero level for the strain gauges during the investigation was the mid thoracic line measured at the sternal insertion of the fourth rib. The electrical standards of the manometers were calibrated in connection with each investigation using a hydrostatic standard corresponding to a pressure of 30 and 100 mm Hg above the zero line for the venous and arterial sides respectively. An electrocardiogram (ECG) was recorded simultaneously with the pressure curves, a lead was chosen which displayed the most clear cut P waves.

The *heart rate* was calculated from the mean of ten atrial or ventricular complex distances. The *stroke volume* was obtained by dividing CO by the ventricular rate as measured from ECG during the blood sampling.

Body surface area (BSA) was ob

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* Eschweiler & Co, Kiel, Germany.

Hemodynamic findings during an orthostatic test in patients with complete heart block

Patients with a slow pulse rate e g patients with complete heart block (CHB) may have difficulty in adjusting their circulation to a rapid change from a supine to standing position This is indicated by the higher percentage of patients experiencing dizziness on rising after CHB had been established than before it appeared This has been discussed in chapter III Now that it is possible to increase the pulse rate with an artificial pacemaker it seemed worthwhile studying the hemodynamic reaction to an orthostatic test in patients with CHB

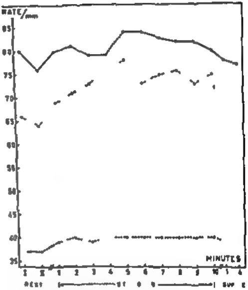

Fig 1a Atrial rate ——— and ventricular rate in patients with complete heart block (CHB) at catheterization group II and heart rate in patients having had a transient CHB but with sinus rhythm at catheterization group I Rest I and II denotes the means of the two resting values obtained 30 and 40 minutes after catheter introduction The figure shows the mean values during the orthostatic test and 1 and 4 minutes after the patients had been tilted back to supine position

A Results

Resting values

As mentioned in chapter V the patients rested half an hour after the catheters had been introduced Thirty and forty minutes after the catheter had been introduced an electrocardiogram (ECG) was recorded and pressures and flows were registered The small differences obtained in the various hemodynamic parameters on these two occasions show that the reproducibility of the method was good The low values obtained indicate that the patients were in a basal state when the orthostatic test began The two resting values are denoted as rest I and rest II in figures 15—19 The individual values are given in the Appendix table II There was a slight fall in the atrial rate both in group B which consisted of patients

Values obtained 30 minutes after the end of exercise were used as resting values before the *atropine test*. The patient was given a rapid intravenous injection of 0.1 mg atropine sulfate/10 kg body weight. Pressures and ECG were recorded every other minute and CO was determined 2 and 10 minutes after the injection.

The blood removed for samples was approximately replaced by a continuous intravenous saline infusion. Four patients fainted or almost fainted during the orthostatic test but no severe *complications* occurred during the catheterization. Details are given in chapters VI, VII and VIII and in the Appendix, tables B, C and D.

CHAPTER VI

Hemodynamic findings during an orthostatic test in patients with complete heart block

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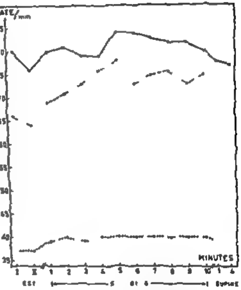

Fig 15 Atrial rate ——— and ventricular rate in patients with complete heart block (CHB) at catheterization group II and heart rate in patients having had a transient CHB but with sinus rhythm at catheterization group T Rest I and II denotes the means of the two resting values obtained 30 and 40 minutes after catheter introduction The figure shows the mean values during the orthostatic test and 1 and 4 minutes after the patients had been tilted back to supine position.

A Results

Resting values

As mentioned in chapter V the patients rested half an hour after the catheters had been introduced Thirty and forty minutes after the catheter had been introduced an electrocardiogram (ECG) was recorded and pressures and flows were registered The small differences obtained in the various hemodynamic parameters on these two occasions show that the reproducibility of the method was good The low values obtained indicate that the patients were in a basal state when the orthostatic test began The two resting values are denoted as rest I and rest II in figures 15—19 The individual values are given in the Appendix table B There was a slight fall in the atrial rate both in group II which consisted of patients

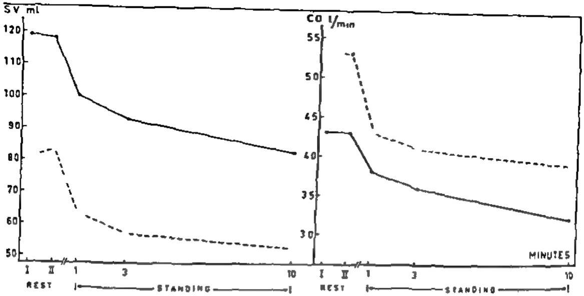

Fig 16 Stroke volume (SV) and cardiac output (CO) in group B ——— and group T ----- at rest and after 1, 3 and 10 minutes in the standing position Symbols as in fig 15

with CHB at examination and in group T, consisting of patients who had had a CHB but showed sinus rhythm at examination (see fig 1 and chapter V for details) This difference was significant in group T (0 01>P >0 001) but not in group B (P>0 05) The ventricular rate in group B showed no change between rests I and II nor did the aortic pressures In group T there was an insignificant decrease of the systolic and diastolic pressures (P>0 05) while the pulse and mean pressures were mainly unchanged Neither group B and nor group T showed any changes in the cardiac output (CO)

Orthostatic test

The Appendix table B gives individual observations, mean and standard deviation of the various hemodynamic parameters before and during the orthostatic test which was performed as described in chapter V

One patient (case 15 in the Appendix, table A) in group B became pale and dizzy after 10 minutes standing The orthostatic reaction disappeared immediately after the patient had been tilted back In group T there were two patients (cases 25 and 27 in table A) with a similar complication but the test could be completed Another patient in group T (case 20) fainted after three minutes standing but recovered immediately after being tilted back

During the orthostatic test the *atrial rate* (fig 15) which was higher at rest in group B than in group T rose in both groups in group T from 64 to 78/min and in group B from 76 to 84/min After five minutes standing there was a slight fall of the atrial rate in both groups After the patients had been tilted back the original atrial rate was resumed within one minute

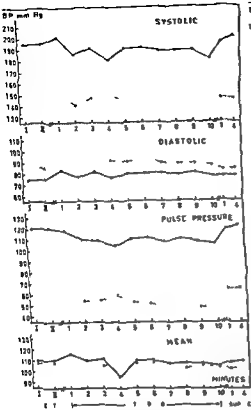

Fig 17 Blood pressure in group B ——— and group T .... at rest during the orthostatic test and 1 and 4 minutes after the patients were tilted back Symbols as in fig 15

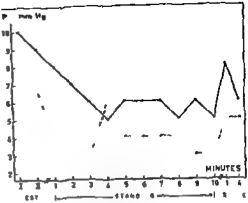

Fig 18 Mean right atrial pressure ($\bar{P}_{RA}$) in group B ——— and group T .... at rest during the orthostatic test and 1 and 4 minutes after the patients were tilted back. Symbols as in fig 15

The *ventricular rate* (fig 15) rose in both groups In group T the same values were obtained as for the atrial rate In group B the original value of 37/min rose to 40/min after two minutes standing ($P<0.001$)

Cardiac output (CO) was lower in group B (fig 16) than in group T (4 3 and 5 3 l/min respectively) but both groups displayed a fall to 3 2 and 3 9 l/min The corresponding figures for *cardiac index* (CI) were 2 4 and 2 9 l/min and 1 8 and 2 1 l/min

Owing to the decrease of CO and the increase of pulse rate the *stroke volume* (SV) fell in group B from 118 to 83 ml and in group T from 88 to 53 ml (fig 16)

The *systolic blood pressure* (fig 17) in the aorta fell about 10 mm Hg in group B after two minutes standing and then levelled off The original value was resumed one minute after tilting back A similar pattern was observed in group T The *diastolic blood pressure* (fig 17) showed a slight increase in both groups especially early in the orthostatic test It follows that the *pulse pressure* (fig 17) fell in both groups The *mean pressure* (fig 17) showed an initial increase in both groups but later fell slightly

The *mean right atrial pressure* ($\bar{P}_{RA}$) fig 18 which at rest was 2—3 mm Hg higher in group B than in group T fell in group B from 9 to 5 mm Hg A similar drop was observed

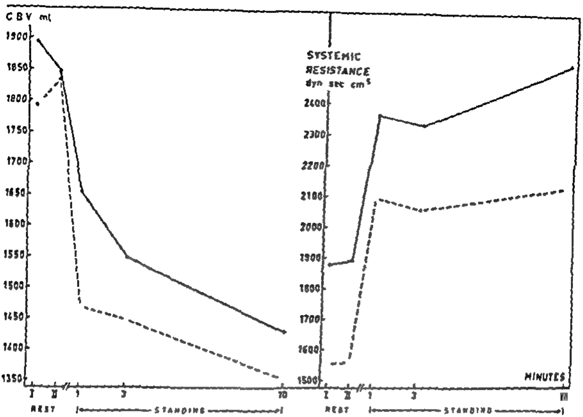

Fig 19 Central blood volume (CBV) and systemic peripheral resistance in group B ——— and group T ------ at rest and after 1 3 and 10 minutes in the standing position Symbols as in *fig 15*

in group T but here the lower level was reached immediately after tilting

The *systemic peripheral resistance* (fig 19) in group B rose after one minute standing from 1891 to 2366 dyn sec cm^{-5} There was a further rise at the end of the orthostatic test to 2536 dyn sec cm^{-5} In group T the resting resistance was lower 1562 dyn sec cm^{-5}, but showed a pattern similar to group B, with a rise to 2138 dyn sec cm^{-5} after 10 minutes standing

The *central blood volume* (CBV) fell steadily in group B from an original value of 1848 ml to 1654 ml after 1 minute standing 1549 ml after 3 minutes and 1428 ml after 10 minutes standing (fig 19) In group T the initial fall was more pronounced, from 1837 ml at rest to 1468 after 1 minute standing and there was a further decrease to 1351 ml after 10 minutes standing

Appearance time, peak time, build up time and *mean transit time* showed no significant changes during the orthostatic test All these parameters were longer in group B than group T MTT for example being 26 secs and 21 secs respectively as seen in the Appendix table B (0 05 > P > 0 01)

B Discussion

Resting values The low values obtained at rest in groups B and T in

dicate that the patients were in a basal state yet the atrial rate was higher in group B 76 beats/min than in group T 64 beats/min This difference persisted later during the catheterization (P=0 05) This finding is surprising since one would expect a lower atrial rate secondary to an increased vagal tone in group B as a result of the increased aortic pressure Two possible explanations are that the higher atrial rate in group B 1) is a compensatory mechanism for the low CO and 2) is a result of the Bainbridge reflex The latter explanation is supported by the finding of a higher $\bar{P}_{RA}$ in group B than in group T

Orthostatic test A change of body posture from recumbent to erect position is accompanied by profound circulatory alterations and adjustments A constant finding is a decrease of the CO Coe et al (29) observed a fall by 20 % when convalescent not acutely ill ward patients were tilted with head up 30° Stead et al (122) examined five normal subjects in the recumbent position and tilted to an angle of 70° from the horizontal with the feet resting against an upright foot support they found a fall in mean CI from 3 2 to 2 4 l/min (25 %) This pattern seems to appear irrespective of the heart rate since Stollreiter (123) reported similar results in patients with second degree A V block while in the present material the patients with CHB showed a fall in CO from 4 3 to 3 2 l/min (26 %)

It is noticeable that one patient out of nineteen with CHB became pale and dizzy after 10 minutes standing while this occurred in two patients with sinus rhythm and a third patient in group T fainted after three minutes standing These patients usually displayed a pronounced decrease of systolic diastolic and mean aortic blood pressure and the pulse pressure also decreased The atrial and ventricular rate remained largely unchanged The $\bar{P}_{RA}$ decreased markedly in one of the patients in group T (case 27) while the change in the other patients was slight In the patient in group T who fainted CO determination was being performed when syncope appeared the CO was 1 7 l/min compared with a resting value of 4 9 l/min The corresponding SVs were 31 and 88 ml There was a fall of CO and SV in the other three patients too during the orthostatic reaction but not as pronounced and no more than the means for the whole group The CBV fell while there was a rise in the systemic peripheral resistance The changes in these two parameters did not differ from the means of the group either except in the patient who fainted Sundin (126) showed that tilting of healthy subjects to 50° induces a rise in the noradrenaline excretion It is possible that the patients who experienced an orthostatic reaction in the present material had an unsatisfactory noradrenaline response

Except for the rise in peripheral resistance these results agree with those published by Weissler et al (133) who induced postural syncope by a 60° head up tilt and oral administration of sodium nitrite These authors were able to reverse the syncopal reaction

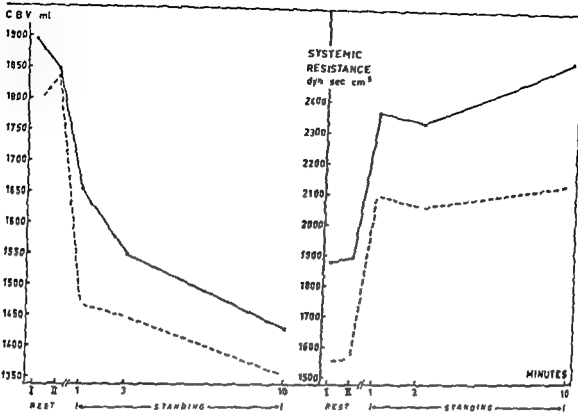

Fig 19 Central blood volume (CBV) and systemic peripheral resistance in group B ——— and group T - - - - at rest and after 1 3 and 10 minutes in the standing position Symbols as in fig 15

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Appearance time, peak time, build up time and *mean transit time* showed no significant changes during the orthostatic test All these parameters were longer in group B than group T MTT for example being 26 secs and 21 secs respectively as seen in the Appendix, table B ($0.05 > P > 0.01$)

B Discussion

Resting values The low values obtained at rest in groups B and T in

Hemodynamic findings during exercise in patients with complete heart block

It has been shown that cardiac output (CO) is rate dependant (5 13 43 71) especially at extreme ventricular rates but to a varying degree in different patients probably depending on the degree of myocardial impairment (92) Benchimol et al (6) exercising patients at fixed ventricular rates of 50 70 and 90 beats/min found a maximal increase in CO at 70 and 90 beats/min and Åstrand and Landegren (1) obtained results indicating an increased physical work capacity at the higher stimulation rates when exercising seven patients with artificial pacemakers set at 27—48 67—72 and 92—105 impulses/min

It seems therefore that the slow ventricular rate in patients with complete heart block (CHB) is a factor which limits the exercise capacity It is a common clinical concept that adult patients with CHB have a comparatively stable and slow pulse rate but it is also known that patients with congenital heart block can increase their ventricular rate on exercise (98)

In order to make a detailed study of the hemodynamic response to exercise patients with CHB were investigated during an exercise test first in the sitting and on a later occasion in the supine position

A Results

An *exercise test* on a bicycle ergometer with the patients *in the sitting position* was if possible performed at the follow up examination It was found that 3 patients with CHB could not exercise on the ergometer for different reasons 1 patient was too old 1 had sequelae of a stroke and 1 could not cooperate because of an advanced cerebral arteriosclerosis In the 26 patients able to perform the exercise test the mean maximal working capacity calculated as described in chapter II, was found to be 323 kpm/min standard deviation (SD) 172 Among these patients there were 18 male and 8 female patients The mean age was 71 and 50 years respectively in these groups and the corresponding maximal working capacity 335 (SD 172) and 295 (SD 181) kpm/min

An *exercise test in the supine position* was made in 19 patients with CHB twelve of those in best condition being selected at the follow up examination and seven coming *from other* hospitals (fig 1) As it is usually possible to *perform* a heavier exercise in the *sitting than* in the supine position the work loads obtained at the first test in the sitting position were slightly

(with CO rise as a result) by means of antigravity suit inflation or negative pressure breathing while atropinization did not alter the CO response. They claimed that the major circulatory event of vasodepressor syncope *would appear to be loss of peripheral* resistance and its occurrence in the face of inability of the heart to compensate by an increase in CO, this probably being caused by a limited inflow of blood to the heart.

There are various explanations for the differences in *systemic peripheral* resistance in the present material and that published by Weissler et al (133). The most important reason is probably that the sodium nitrite used in Weissler's *material may have affected the* peripheral resistance. This is supported by a detailed study of Lagerlöf et al (81) in patients who were tilted from the horizontal to the upright position. The results of these authors agree with those in the present material including a rise in the peripheral resistance.

It seems, then, as if patients with a chronic CHB are less prone to develop postural syncope *during an orthostatic* test than are patients in a reference *material with sinus rhythm*. A possible explanation is that the high $\bar{P}_{RA}$ secondary to the low ventricular rate accompanying CHB provides a satisfactory inflow of blood to the heart, since according to Weissler et al (133) a limited inflow of blood is a causative factor in producing vasodepressor syncope. It is possible that the circumstances are different in patients with a newly established CHB, *for it is a* clinical impression that these patients often have a *feeling of dizziness or* vertigo on rising suddenly *from a su*pine to an erect position.

Summarizing: patients with CHB subjected to an orthostatic test showed a slight *increase in atrial and ventricu*lar rate, CO and SV decreased as did the systolic blood pressure, pulse pressure and mean pressure, while the diastolic blood pressure showed a slight *increase. The $\bar{P}_{RA}$ fell as did CBV* while the peripheral resistance rose. There were fewer orthostatic reactions in the patients with CHB than in the reference material, all with sinus rhythm.

CHAPTER VII

Hemodynamic findings during exercise in patients with complete heart block

It has been shown that cardiac output (CO) is rate dependent (5 13 43 71) especially at extreme ventricular rates but to a varying degree in different patients probably depending on the degree of myocardial impairment (92) Benchimol et al (6) exercising patients at fixed ventricular rates of 50 70 and 90 beats/min found a maximal increase in CO at 70 and 90 beats/min and Åstrand and Landegren (1) obtained results indicating an increased physical work capacity at the higher stimulation rates when exercising seven patients with artificial pacemakers set at 27—48 67—72 and 92—105 impulses/min

It seems therefore that the slow ventricular rate in patients with complete heart block (CHB) is a factor which limits the exercise capacity It is a common clinical concept that adult patients with CHB have a comparatively stable and slow pulse rate but it is also known that patients with congenital heart block can increase their ventricular rate on exercise (98)

In order to make a detailed study of the hemodynamic response to exercise patients with CHB were investigated during an exercise test first in the sitting and on a later occasion in the supine position

A Results

An *exercise test* on a bicycle ergometer with the patients *in the sitting position* was if possible performed at the follow up examination It was found that 3 patients with CHB could not exercise on the ergometer for different reasons 1 patient was too old 1 had sequelae of a stroke and 1 could not cooperate because of an advanced cerebral arteriosclerosis In the 26 patients able to perform the exercise test the mean maximal working capacity calculated as described in chapter II was found to be 323 kpm/min standard deviation (SD) 172 Among these patients there were 18 male and 8 female patients The mean age was 71 and 70 years respectively in these groups and the corresponding maximal working capacity 335 (SD 172) and 295 (SD 181) kpm/min

An *exercise test in the supine position* was made in 19 patients with CHB twelve of those in best condition being selected at the follow up examination and seven coming from other hospitals (fig 1) As it is usually possible to perform a heavier exercise in the sitting than in the supine position the work loads obtained at the first test in the sitting position were slightly

(with CO rise as a result) by means of antigravity suit inflation or negative-pressure breathing, while atropinization did not alter the CO response They claimed that the major circulatory event of vasodepressor syncope would appear to be loss of peripheral resistance and its occurrence in the face of inability of the heart to compensate by an increase in CO, this probably being caused by a limited inflow of blood to the heart

There are various explanations for the differences in systemic peripheral resistance in the present material and that published by Weissler et al (133) The most important reason is probably that the sodium nitrite used in Weissler s material may have affected the peripheral resistance This is supported by a detailed study of Lagerlof et al (81) in patients who were tilted from the horizontal to the upright position The results of these authors agree with those in the present material, including a rise in the peripheral resistance

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Summarizing patients with CHB subjected to an orthostatic test showed a slight increase in atrial and ventricular rate, CO and SV decreased as did the systolic blood pressure pulse pressure and mean pressure while the diastolic blood pressure showed a slight increase The $\bar{P}_{RA}$ fell as did CBV while the peripheral resistance rose There were fewer orthostatic reactions in the patients with CHB than in the reference material all with sinus rhythm

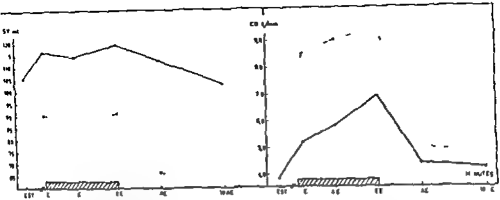

Fig 21 Stroke volume (SV) and cardiac output (CO) in group B ——— and group T ---- at rest during and after exercise Symbols as in fig 20

high initially in group B with a mean of 106 ml Nevertheless there was a further rise during exercise except in the patient (case 11) who had to stop after three minutes and in cases 12 18 and 19 for which the increase in ventricular rate was pronounced An initial rise was later partly reversed in cases 3 4 and 17 In these cases the ventricular rate was slow to rise In group T SV also increased from 73 ml at rest to 91 ml after eight minutes exercise

The *aortic systolic blood pressure* fig 22 which was high in group B at rest increased further during exercise but had returned to the resting level *four minutes* after exercise It was noted that six patients had a fall in systolic blood pressure just after the beginning of exercise this was subsequently restored in one case and surpassed in three cases while in two the resting level was not reached In group T there was a slight systolic fall at the beginning of exercise in two cases The *diastolic pressure* fig 22 showed a moderate increase during exercise but individual differences were great with both increases and decreases The *pulse pressure* fig 22 which was high at rest in group B 122 mm Hg showed a further increase during exercise but only moderately so and individual variations were great here as well In group T the pulse pressure rose in all but one case The *mean aortic* pressure fig 22 also displayed varying patterns but the mean values showed an increase

The *mean right atrial pressure* (P_{RA}) fig 23 was increased at rest in group B 8 mm Hg and rose further during exercise in all cases sometimes to as much as 28 mm Hg The highest levels were usually found in the patients who could not complete the full eight minutes In group T there was also an increase of P_{RA} but less pronounced than in group B

The *systemic peripheral resistance* showed a gradual decrease in group B from a resting value of 2 062 dyn sec cm⁻⁵ to 1 586 after one minute s exer

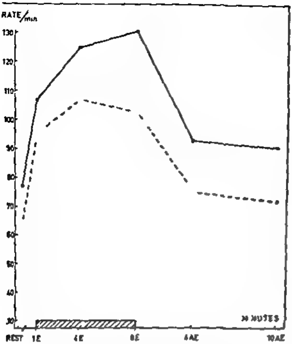

Fig 20 Atrial rate ——— and ventricular rate - - - - in patients with complete heart block (CHB) at catheterization group B and heart rate ········ in patients having had a transient CHB but with sinus rhythm at catheterization group T The figure shows the mean values obtained at rest during exercise E and after exercise AE 1E denotes values obtained at 1 minute of exercise 4AE values obtained at 4 minutes after exercise //////// denotes exercise

decreased when the patients were exercised in the supine position during the catheterization study Since the maximal working capacity had previously been determined for all the patients participating in the catheterization, it seemed reasonable in this descriptive study to compare the individual exercise responses despite the different work loads Individual observations, mean and SD are given in the Appendix, table C Four patients were unable to complete the full eight minutes, one of them stopped already after one minute because of dyspnea and fatigue, one after three minutes because of cramp in his right leg and two after four minutes, because of fatigue

The *atrial rate*, fig 20 usually did not reach a steady state in group B which includes patients with CHB during catheterization (patient numbers 1—19 in the Appendix, table C), and ten minutes after exercise the rate had still not returned to the preexercise level Patients in group T, who had had a transient CHB but showed sinus rhythm during catheterization had *lower resting* values and the *increase* during exercise was less pronounced than in group B, though in this group, too, preexercise levels had not been reached ten minutes after exercise

The *ventricular rate* fig 20 at rest was 37 beats/min in group B No steady state was reached in many cases and the means constantly rose to 47 beats/min after one minute s exercise and 61 beats/min after eight minutes The range was great the highest increase amounted to 58 beats/min while two cases even displayed a slight decrease from 31 to 30 beats/min Four minutes after exercise the ventricular rate had already fallen almost to preexercise level

Cardiac output (CO) fig 21 was low in group B already at rest (3 9 l/min) but rose during exercise in all cases with the exception of the patient (case 11) who had to stop after three minutes All patients unable to complete the exercise had only a slight rise in CO

Stroke volume (SV) fig 21 was

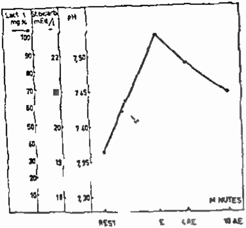

Fig 25 Arterial lactate concentration in mg/100 ml standard bicarbonate in mEq/l and pH in group B before at the end of and after exercise See further legend to fig 20

took longer for the patients in group B to reach the resting level

The *arterio venous oxygen difference* (a v)O_2 difference fig 24 at rest showed a mean of 6 4 ml/100 ml in group B with a dramatic rise during exercise to 13 8 ml/100 ml After exercise there was a rather rapid fall towards rest levels

The *arterial oxygen tension* (PaO_2) was normal at rest in group B 84 mm Hg but decreased during exercise to 77 mm Hg

The *arterial pH* fig 25 fell from 7 44 at rest to 7 39 during exercise but had approximated to the rest level ten minutes after exercise 7 43 For *standard bicarbonate* on the other hand the decrease during exercise (from 22 1 to 18 8 mEq/l) was not restored ten minutes after exercise when the mean was 19 6 mEq/l (fig 25) The *lactate concentration* (fig 25) curve showed a peak increase at the end of exercise but here too original values were not reached ten minutes after exercise

B Discussion

Patient histories as well as the values given in the Appendix table A on the physical working capacity and the hemodynamic results of the exercise test reported in this chapter show that patients with CHB have a reduced functional capacity This statement is also illustrated by a comparison between patients with CHB at examination, group B and patients in group T comprising patients who had had a CHB but showed sinus rhythm at examination (Individual values are given in the Appendix table C) Restricting the comparison because of differences in age and sex distribution to male patients 60 years old or more shows differences in the work load at maximal intensity at exercise in the sitting position (314 kpm/min in group B and 369 in group T) although the difference is not significant The maximal work load of male patients aged 60 years or more in group B was much lower than Granath et al (50) observed in their healthy old men Furthermore the physical working capacity for men below 60 years in group T was lower than that found by Malmborg (91) for his controls

Although it is reasonable to suppose that the circulatory system is the limiting factor a spirometry was done to rule out the pulmonary system as a possible limiting organ Apart from a general decrease of the maximal vol

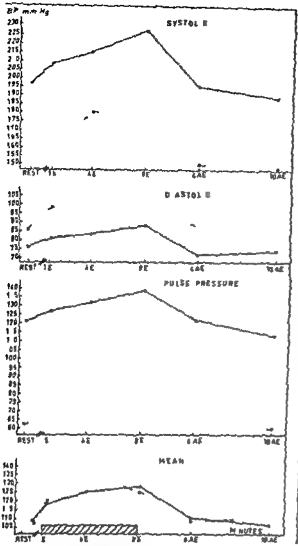

Fig 22 Blood pressure in group B ——— and group T at rest during and after exercise Symbols as in fig 20

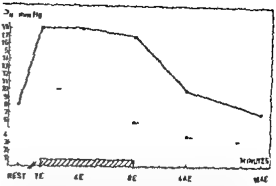

Fig 23 Mean right atrial pressure (P_{RA}) in group B ——— and group T at rest during and after exercise Symbols as in fig 20

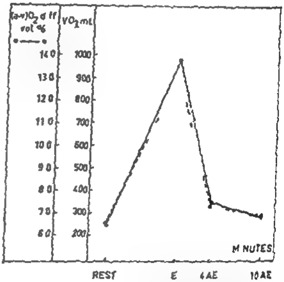

Fig 24 Arterio venous oxygen difference (a v)O_2 diff in ml per 100 ml and oxygen consumption (VO_2) in ml/min in group B before at the end of and after exercise See further legend to fig 20

cise and 1 257 dyn sec cm^{-5} after eight minutes In group T there was an instant drop at the beginning of exercise In both groups resting values were reached ten minutes after exercise

The *central blood volume* (CBV) rose in group B from a resting value of 1 679 ml to 2 345 ml after eight minutes exercise A similar pattern was observed in group T

The *mean transit time* (MTT) at rest was longer in group B than in group T and during exercise it became shorter in both groups

The *oxygen consumption/min* (VO_2) rose in group B fig 24 from a resting value of 250 ml to 920 ml during the last minutes of exercise Similar values were found in group T However at

through the sympathetic nervous system and an increase of the vasoactive catecholamine concentration in the blood. An increase of the filling pressure of the right ventricle was reflected in the P_{RA} rise as shown in fig 23. Segel et al (112) have shown that the pulmonary wedge pressure which mirrors the filling pressure of the left ventricle is also increased during rest in patients with CHB and shows a further increase during exercise. The blood catecholamine concentration is also relevant for SV since a SV increase was found in patients with CHB during the administration of adrenaline and isopropylnoradrenaline (66). Similar findings although not constantly have been reported by Stack et al (118) after isopropylnoradrenaline. Administration of these catecholamines also resulted in an increase in the ventricular rate. In an attempt to predict the response of ventricular rate during exercise the ventricular rate at rest was plotted against the increase during exercise but no correlation was found.

The response of the patient with CHB to exercise is of no value in individual cases for the prognosis quo ad vitam. This is shown by patient number 19 (clinical and hemodynamical data are given in the Appendix tables A and C) who responded well to exercise but died 11 days later in connection with an Adams Stokes attack.

Comparison with healthy old men

Since the physical working capacity varies with age group T in the present material cannot be compared with group B because its age distribution is not similar. Recently Granath et al (50) studied the circulation in healthy old men by means of right heart catheterization at rest and during exercise. The patients from Stockholm were 61—83 years old with a mean age of 71 years. The Malmö material includes 14 male patients with CHB aged 60 years or more mean age 70 years; this group is thus suitable for a comparison with the Stockholm controls. The 14 patients are presented in the Appendix, table A as numbers 1—14.

Granath et al (50) observed an increase in heart rate from a rest value of 67 beats/min to 130 beats/min during the heaviest load. Corresponding values in the Malmö material were 38 and 58 beats/min for the ventricular rate and 78 and 130 beats/min for the atrial rate. The differences in atrial rate constantly observed in the present material with a higher atrial rate at rest in group B than in group T thus holds good in comparison with the Stockholm controls.

$\dot{V}O_2$ at rest was similar in the present material 263 ml to the Stockholm controls 255 ml while $\dot{V}O_2$ during exercise in the present material was 911 ml as against 958 ml during the Stockholm controls first work load which averaged 278 kpm/min (range 200—400). Their second load averaged 550 kpm/min (range 400—800) and $\dot{V}O_2$ was then 1 464 ml.

Granath et al (50) used the direct Fick method for determining CO and found 5.78 l/min at rest and 10.29 and 13.08 l/min at the first and second

untary ventilation (MVV_F) there were usually no major disturbances of the pulmonary function (individual observations are given in the Appendix, table A). The spirometry values support the assumption that the pulmonary system was not the limiting factor. Case 17 was an exception and she had a very low *physical working capacity*.

In one patient with CHB (case 1 in the Appendix, table A) the hemoglobin value was lower than normal but in the other cases the values were within normal ranges or only slightly decreased. Since there were no signs of hematological disorders, it seems reasonable to assume that no anemia of any real importance for the results was present in the material. This further entitles us to concentrate the search for the limiting factors to the heart itself.

As shown in fig 20 the ventricular rate increased during exercise, sometimes markedly, in most cases with CHB ($P<0.001$). The ventricular rate in CHB is apparently rather variable at least in some cases. This is also supported by Gilchrist's (46) finding of spontaneous variations in pulse rate as mentioned in chapter IV. It is known that the ventricular rate may double during exercise in young patients with CHB, probably of congenital origin (61, 98). In older patients Segel et al (112) reported the ventricular rate response to be much less pronounced but these authors used a very light exercise.

As fig 21 and the Appendix, table C show, the SV and stroke index (SI) which were large at rest, usually showed a further increase during exercise. Segel et al (112) also observed an increase of SI in their material.

CO was low at rest, as shown in fig 21 and the Appendix, table C. Low resting values in patients with CHB have also been reported by other authors (5, 44, 87, 112, 118). The low CO is mainly occasioned by the low ventricular rate, since CO rises when the ventricular rate is artificially increased with a pacemaker (13, 112, 117).

The CO rise on exercise in the present study can thus be accounted for by the increase in both ventricular rate and SV. In a few cases (for details see the Appendix, table C) the CO rise was non existent or very small, as was the SV rise. There were good clinical reasons to suspect a seriously damaged myocardium in these cases. Torresani et al (130) concluded that a normal or low SV despite bradycardia is indicative of myocardial insufficiency.

The adjustment to exercise was not confined to the CO rise. The tissues oxygen extraction from the blood was markedly increased, as shown by the rise in the $(a-v)O_2$ difference from a mean of 6.4 ml/100 ml at rest to 13.8 at the end of exercise. Despite these regulatory mechanisms there was a pronounced increase in arterial lactate concentration during exercise in the patients with CHB indicating a high degree of anaerobic metabolism.

An SV increase during exercise can be obtained in at least two ways: 1) increase of the filling pressure and 2) direct action on the myocardium

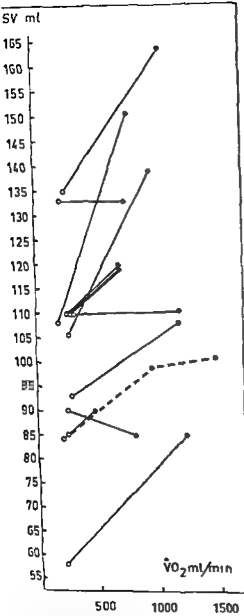

Fig 2 Stroke volume in relation to oxygen consumption ($\dot{V}O_2$) in 10 patients in group B being 60 years or older and in whom $\dot{V}O_2$ was obtained during the last minutes of exercise ○ rest ● = exercise ——— denotes mean values - - - - denotes mean values obtained by Granath et al (50) in healthy old men exercised in recumbent position at two different loads See further legend to fig 20

corresponding initial diastolic pressure was 4 3 mm Hg

This comparison of CHB patients with a material of healthy old men shows that CHB brings about a hypokinetic circulation with a decreased CO because of the slow ventricular rate and despite an increased SV The (a v)O₂ difference is increased both at rest and during exercise as is the $\bar{P}_{RA}$ It should be remembered that the CHB patients selected for catheterization were those in the best clinical condition so that a comparison between Granath s et al (50) healthy old men and the total CHB material would be still more unfavorable than the above *Summarizing* a physical exercise test in the sitting position in patients with CHB showed a decreased working capacity

Exercise in the supine position resulted in a marked rise of the atrial rate in patients with CHB The ventricular rate rose too but less so CO was low at rest but increased during exercise because both ventricular rate and SV rose as did the aortic blood pressure $\bar{P}_{RA}$ was high at rest but increased markedly during exercise while the systemic peripheral resistance declined $\dot{V}O_2$ showed a more than threefold rise and the (a v)O_2 difference which was high at rest was more than doubled during exercise Arterial pH fell as did standard bicarbonate but pH was normalized

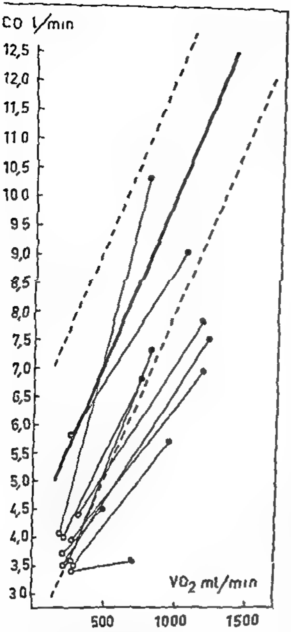

Fig 26 Cardiac output (CO) in relation to oxygen consumption (VO_2) in 10 patients in group B being 60 years or older and in whom VO_2 was obtained during the last minutes of exercise ○=rest ●=exercise ——— denotes the regression line and - - - - the 95 % confidence limits obtained by Granath et al (50) in healthy old men exercised in recumbent position See further legend to fig 20

work loads, respectively The individual CO observations in the present material are plotted against the VO_2 in fig 26, together with the regression line and 95 % confidence limits obtained by Granath et al (50) Despite the higher SVs in the present material (fig 27) CO at a particular VO_2 is lower both at rest and during exercise There is also a difference between the two materials in the $(a-v)O_2$ difference, with a rest value of 6 8 ml/100 ml rising to 13 7 in the present material as against 4 5 rising to 9 4 ml/100 ml during the first load and to 11 2 during the second load in the Stockholm material

The arterial lactate concentration at rest in patients with CHB was 34 mg/100 ml and rose to 106 mg/100 ml at the end of exercise For eight healthy males aged 70—79 years and exercised in the sitting position Strandell (124) obtained a resting value of 17 mg/100 ml this rose to 35 at a work load of 300 kpm/min and to 68 mg/100 ml at 900 kpm/min Even allowing for the fact that exercise in the supine position produces higher lactate concentration levels than when the same exercise is done in the sitting position (124) the CHB patients showed higher lactate values than Strandell's healthy old men however, the lactate was determined differently in the two studies

There is a difference in the P_{RA} too the present material had 8 mm Hg at rest, rising to 18 mm Hg while the Stockholm controls had a mean of [illegible] mm Hg at rest and a maximal end diastolic pressure in the right ventricle of 13 5 mm Hg during exercise The

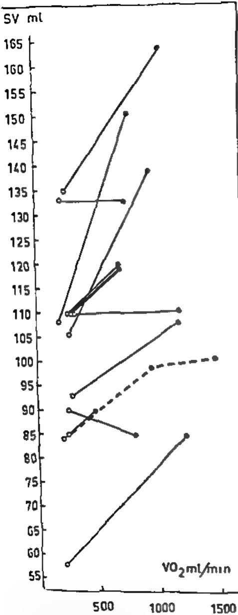

Fig 7 Stroke volume in relation to oxygen consumption (VO_2) in 10 patients in group B being 60 years or older and in whom VO_2 was obtained during the last minutes of exercise ○ = rest ● = exercise ——— denotes mean values - - - denotes mean values obtained by Granath et al (50) in healthy old men exercised in recumbent position at two different loads See further legend to fig 20

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sooner after exercise The lactate concentration showed a peak at the end of exercise

The factors limiting the physical exercise in CHB patients are discussed, a comparison with healthy old men indicates an impaired circulatory response in patients with CHB

The response of the patient with CHB to exercise is of no value in individual cases for the prognosis quo ad vitam

Hemodynamic effects of atropine in patients with complete heart block

Atropine is not infrequently administered to patients with complete heart block (CHB) especially when complicated with Adams Stokes attacks (65). Since the literature on the mechanism of the action of atropine is sparse, contradictory and incomplete, a study was made of the effect of atropine administration to patients with CHB.

A. Results

The Appendix (table D) gives the individual observations, mean and standard deviation before, two and ten minutes after the injection of atropine sulfate in a dose of 0.1 mg/10 kg body weight as described in chapter V.

The *atrial rate* (fig. 28) at rest was higher (85 beats/min) in patients with CHB at examination (group B) than in group T (69 beats/min), which consisted of patients who had had a CHB but showed sinus rhythm at examination. Two minutes after the atropine injection the atrial rate had increased in both groups to 101 and 87 beats/min respectively and persisted at this level largely unchanged. The increases are significant ($P < 0.001$) and ($0.01 > P > 0.001$) respectively. The *ventricular rate* (fig. 28) showed the same values as those given for the atrial rate in

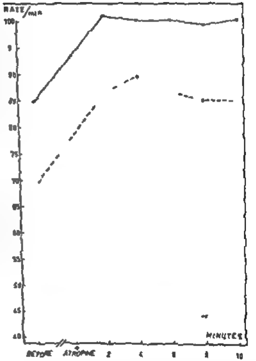

Fig. 28. Atrial rate ——— and ventricular rate ---- in patients with complete heart block (CHB) at catheterization, group B, and heart rate ···· in patients having had a *transient* CHB but with sinus rhythm at catheterization, group T. The figure shows the mean values obtained before, 2, 4, 6, 8 and 10 minutes after the i.v. injection of 0.1 mg atropine sulfate/10 kg b.w., which is denoted by ↑.

group T, while in group B there was an increase from 41 to 45 beats/min

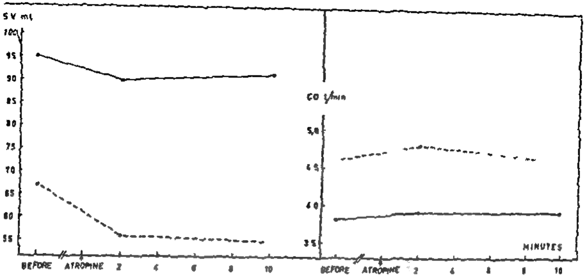

Fig 29 Stroke volume (SV) and cardiac output (CO) in group B ——— and group T - - - before and after atropine injection Symbols as in fig 28

two minutes after injection ($0.05 > P > 0.01$), the complete heart block remained

Cardiac output (CO) fig 29, showed no significant change This means that there was a decrease in *stroke volume* (SV), fig 29, in group B from 95 to 90 ml and in group T from 67 to 55 ml

Fig 30 shows that the *systolic blood pressure* decreased continuously in group B from 179 to 167 mm Hg 10 minutes after the injection, and in group T from 150 to 141 mm Hg The *diastolic blood pressure* (fig 30) increased from 72 to 77 mm Hg in group B and from 88 to 92 mm Hg in group T Both groups displayed a return to the initial values 10 minutes after the injection The *pulse pressure* (fig 30) showed a continuous decrease in both groups The *mean pressure* (fig 30) did not change markedly

Fig 31 shows that the *right atrial mean pressure* ($\bar{P}_{RA}$) fell from 7 to 6 mm Hg in group B which is probably significant ($0.05 > P > 0.01$) A significant fall from 5 to 2 mm Hg was observed in group T ($0.01 > P > 0.001$)

The *systemic peripheral resistance* (fig 32) rose slightly in group B and fell in group T two minutes after injection The differences were not significant ($P > 0.05$) The *central blood volume* (CBV), fig 32 decreased in both groups markedly in group T 104 ml ($0.05 > P > 0.01$), than in group B 67 ml ($P > 0.05$) A small but significant ($0.01 > P > 0.001$) change was found in both groups in *mean transit time* (MTT)

B Discussion

It was during a long time traditionally believed that the effect of atropine in CHB was confined to the auricles So well established was this belief that it formed the basis of a test for the differentiation of the extrinsic and intrinsic forms of bradycardia (for a discus

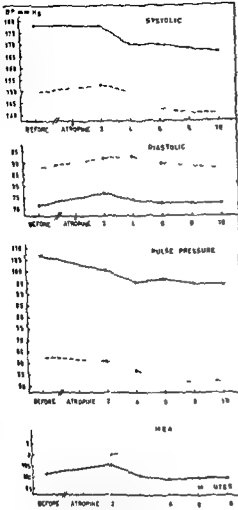

Fig 30 Blood pressure in group B ——— and group T ------ before and after atropine injection Symbols as in fig 28

sion see Gilchrist (45)] Apart from this clinical impression experimental studies were made on animals showing that atropine was without appreciable effect on the ventricles in the completely blocked heart (35) This concept was subsequently contra

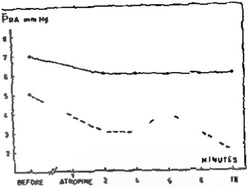

Fig 31 Mean right atrial pressure ($\overline{P}_{RA}$) in group B ——— and group T ------ before and after atropine injection Symbols as in fig 28

dicted Gilchrist (45) obtained a definite increase in ventricular rate in most patients with CHB after the intravenous administration of atropine It is possible that the failure of atropine to increase the ventricular rate in experimental CHB in dogs may be due to the fact that the vagal influence on the heart is very small or that the vagal fibers passing the A V node before reaching the ventricles are destroyed by the procedure used for the production of A V block (36)

It is remarkable that the patients with constant CHB (group B) increased their *atrial rate* after atropine administration almost as much as those with transient CHB (group T) in spite of the higher pre-atropine values in group B The initial decrease of atrial rate after atropine administration described by Schwartz and Pool (109) was not observed in this material probably because this phase was over by the first electrocardiographic (ECG) registration

The mean *ventricular rate* increased

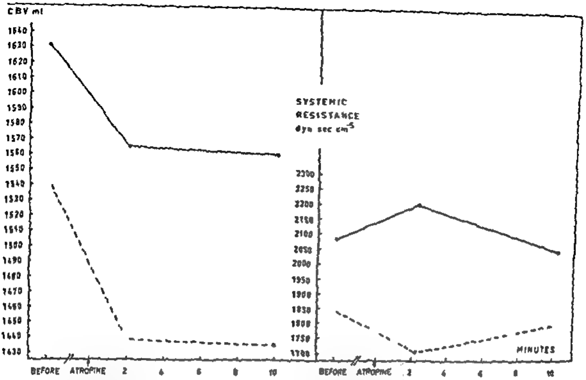

Fig. 32. Central blood volume (CBV) and systemic peripheral resistance in group B ——— and group A - - - - before and after atropine injection. Symbols as in fig. 28.

after atropine in group B as a whole, but the increase was absent or only very slight (1—2 beats/min) in seven patients (cases 2, 3, 5, 8, 9, 14 and 15 in the Appendix, table A). In one patient (case 19 in the Appendix, table A) there was even a decrease due to disappearance of ventricular extrasystoles. Disregarding the extrasystoles, the ventricular rate showed an increase from 37 to 40/min, followed by a decrease to 31/min ten minutes after the injection. It may be assumed that this material comprised two groups, one which responded and one which did not respond to atropine. Excluding then the latter eight patients, atropine administration increased the ventricular rate in the remaining ten patients from 42 to 50 beats/min (0.05>P>0.001).

Gilchrist (45) also observed an increase of ventricular rate after intravenous administration of 2 mg atropine sulfate to ten patients with CHB. He found that the gain in atrial rate was on the whole less variable than the gain in ventricular rate; this agrees with the result in the present study which showed that the increase in ventricular rate varied much and ranged from 0 to 33 beats/min.

The maximal increase in the patients with a bundle branch block type in the ECG was 7 beats/min and 13 beats/min in the patients with a normal QRS duration. It is conceivable, then, that patients with a normal

QRS duration and thus the ventricular pacemaker situated in the vicinity of the A-V node are more influenced by the vagal tone. This is not necessarily so however since three patients with a normal QRS duration showed only a slight increase in ventricular rate (2, 4 and 6 beats/min) and one patient even displayed a slight decrease by 1 beat/min.

The degree of increase in ventricular rate after atropine in the dosage used in this study cannot be used as a prognostic sign. Two patients (cases 2 and 19 in the Appendix Table A) died in connection with Adams-Stokes attacks five months and eleven days respectively after the catheterization and neither of them showed any increase in ventricular rate after atropine, yet the other patients who failed to respond to atropine were quite well at follow-up i.e. at least 14 months after the catheterization.

Despite the increase in ventricular rate there was no significant mean increase in CO in either group B or group T although the individual variations were rather great. Even when the ten patients in group B who all showed an increase in ventricular rate were studied separately no change was found in CO. This means that the SV decreased more so in group T than in group B. The above mentioned patient (case 19 in the Appendix Table A) in whom the ventricular extrasystoles disappeared after atropine resulting in a net decrease of pulse rate showed despite this an initial increase of CO from 4.9 to 5.7 l/min and of SV from 86 to 143 ml.

Berry et al (11) and Kahler et al (72) have studied young healthy subjects in the supine position and reported an increase in CO parallel to the increase in ventricular rate while SV remained constant or decreased. Kelly and Bayliss (75) also found a CO increase in a small group of patients with heart disease. This type of response was not found in the present material possibly because a lower dosage was used despite a definite increase in ventricular rate. Gorlin (49) obtained no CO change in patients with mild valvular heart disease after a dosage similar to the one used here (1.0—1.4 mg of atropine sulfate intravenously). On the other hand Gravenstein et al (52) studying healthy male students observed a CO increase after repeated doses of atropine sulfate totalling about 0.7 mg/70 kg body weight. McGregor and Klassen (92) who observed no CO increase when atropine was given to patients with a fixed paced ventricular rate discussed the mechanism of action of atropine and suggested that the increase in CO which followed atropine administration in sinus rhythm reflects a better ventricular filling as a result of a more forceful coordinated atrial contraction.

In general the reports in the literature on the hemodynamic effect of atropine are rather varied probably due to disparities in vagal tone and age in the materials studied, in the time interval between the administration of the drug and the measurements, or in the mode of administration and dosage.

A further comparison of groups B and T in the present study revealed a similar *aortic blood pressure* pattern, with a *slight decrease of the systolic* blood pressure and the pulse pressure, the diastolic blood pressure returned *to the initial level after a slight in*crease and the mean pressure was mainly unchanged Gravenstein et al (52) observed no blood pressure changes while Gorlin (49) found an insignificant rise in the diastolic pressure

$\bar{P}_{RA}$ decreased from 5 to 2 mm Hg in group T while in group B the initial value of 7 mm Hg decreased to 6 mm Hg This drop is a regular finding (34) in healthy subjects and was also reported by *Kelly* and *Bayliss (75)* for patients with heart disease

CBV showed a slight decrease in both groups *Berry et al (11)* found no change in CBV, in contrast to the results of Weissler et al (132) who observed a rise MTT was longer in group B than in group T both before and after the administration of atropine, a decrease was *observed after atropine*, which agrees with the findings of Weissler et al (132) in young healthy adults

Atropine is frequently given to patients with CHB and patients with Adams Stokes attacks If the Adams Stokes attacks are produced by an increased vagal tone (65), this drug may be of value and this is also true of those patients with *CHB* who respond with a rise in ventricular rate As shown, many patients with CHB display only a very slight change in pulse rate after atropine and it is doubtful whether this drug is of any value in such cases

Summarizing, the intravenous administration of atropine sulfate (0 1 mg/10 kg body weight) to patients with CHB resulted in an increase of the atrial rate the ventricular rate usually rose as well, but less markedly CO remained unchanged The systolic aortic pressure fell slightly, as did $\bar{P}_{RA}$ The *hemodynamic response to atropine* is of no assistance in the prognosis quo ad vitam

Hemodynamic effects of digitalis in patients with an artificial pacemaker

Since different types of response appear simultaneously after the administration of pharmacological agents it is often difficult to determine the contribution of such agents to the total result. A more detailed picture can be obtained if one parameter, e.g. the heart rate, is kept constant. Patients with an artificial pacemaker offer a unique possibility in this respect.

Digitalis was chosen for this study because it has been claimed that this drug exerts its most beneficial effect in cases of auricular fibrillation and that the degree of cardiac slowing is a useful therapeutic index (88, 90). Another reason was that, from a purely therapeutic point of view, it is important to know to what extent patients with an artificial pacemaker may benefit from digitalization. A further incitement was provided by McMichael's lecture on the heart and digitalis. "It has been suggested that new drugs should never be used until their pharmacological effects are fully understood. Had this proscription been effective, digitalis would be prohibited even today, nearly 180 years after Withering's monograph, for we still fall considerably short of full understanding of the mode of action of this remarkable remedy" (93).

A. Methods and material

A catheter was introduced into the brachial artery and the ascending aorta as described in chapter X. A polyethylene catheter, PE 160, was introduced percutaneously via an arm vein to the right atrium or, if this was not possible, a Cournand catheter no. 8 was introduced via a venous cutdown. Through a venous incision on the right or left arm a double lumen catheter[1] was manipulated with the aid of fluoroscopy into the pulmonary artery and the tip was left in the wedge position. Electrocardiogram (ECG) and pressures—PCV, pulmonary artery (PA), right atrium (RA) and aorta—were recorded with the same apparatus and technique as described in chapter X. The pressures were recorded at frequent intervals until a steady state was obtained. Resting cardiac output (CO) was done with the dye dilution technique described in chapter X thirty and forty minutes after the catheters had been put in place. The patients then performed exercise for 8 minutes in the supine

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[1] Cournand Double Lumen 3-1, 150 cm (9 F), United States Catheter and Instrument Corp., Glens Falls, N.Y., USA.

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Atropine is frequently given to patients with CHB and patients with *Adams Stokes attacks If the Adams Stokes attacks* are produced by an increased vagal tone (65), this drug may be of value and this is also true of those patients with CHB who respond with a rise in ventricular rate As shown, many patients with CHB display only a very slight change in pulse rate after atropine and it is doubtful whether this drug is of any value in such cases

Summarizing, the intravenous administration of atropine sulfate (0 1 mg/10 kg body weight) to patients with CHB resulted in an increase of the atrial rate, the ventricular rate usually rose as well but less markedly CO remained *unchanged* The systolic aortic pressure fell slightly as did $\bar{P}_{RA}$ The hemodynamic response to atropine is *of no assistance in the prognosis quo ad vitam*

type and periods of asystole occurred repeatedly in spite of peroral isoprenaline and ephedrine subcutaneously An X ray of the heart showed a predominance of the left ventricle volume 1180/540 ml/sq m BSA No murmur was heard at a pulse rate of 48 beats/min and a blood pressure of 220/85 Hemoglobin (Hgb) 15 3 g per 100 ml (g %) A pacemaker was implanted in November 1964 through a thoracotomy in the usual way (127) The postoperative course was uneventful and the patient was discharged in good condition Postoperative spirometry showed a low maximal voluntary ventilation (MVV$_F$) 60 % of normal but no major changes in other parameters Postoperatively the patient has had no syncopal attacks Fourteen months after the operation he felt well although he became abnormally dyspneic on exertion

Case 2 ♂ born 1889 He had diphtheria as a child and pertussis at 31 years of age Abdominal pains began in 1925 An X ray in 1953 showed signs of a healed gastric ulcer In 1930 a two year period began with multiple attacks of vertigo 1944—1946 seven syncopal attacks occurred ECG showed sinus rhythm and left bundle branch block There was a further period of faintings in 1951 In 1961 he was admitted to hospital because of a new syncope ECG showed CHB and right bundle branch block type Multiple fainting attacks occurred despite treatment with atropine ephedrine isoprenaline and corticosteroids Hgb 14 8 g% Heart volume was calculated to 1080 540 ml/sq m BSA with left ventricular preponderance No murmurs were heard at a pulse rate of 40 beats/min and a blood pressure of 160 60 Because of the frequent Adams Stokes attacks a pacemaker was implanted in November 1963 The postoperative course was uneventful A spirometry was done postoperatively and showed only a slight decrease of vital capacity (VC) forced expiratory volume in 1 sec (FEV$_1$) functional residual capacity (FRC) and total lung capacity (TLC) while FEV$_{1.0}$ in % of VC (FEV %) and lung clearance index (LCI) were normal The patient was well twenty six months after operation and had had no fainting attacks and no signs of cardiac decompensation

Case 3 ♂ born 1919 He had had no rheumatic affliction or diphtheria and no angina pectoris Cholecystectomy was done in 1961 Syncopal attacks began in November 1964 always in connection with physical exercise ECG showed varying degrees of AV block and a left bundle branch block During an exercise test the original sinus bradycardia changed to a 2 1 block with a ventricular rate of 35 beats/min and ventricular premature beats appeared During one such test the patient fainted The physical findings at a pulse rate of 36 beats/min and a blood pressure of 150/60 was a systolic murmur grade 2—3 over the apex Hgb 14 0 g % X ray of the heart revealed a volume of 920/420 ml/sq m BSA A coronary angiography showed slightly irregular walls in both coronary arteries but there were no obstructions No spirometry was done In June 1965 a pacemaker was implanted Multiple episodes of asystole appeared during anesthesia but postoperatively there were no complications and no signs of cerebral damage Seven months after operation no fainting attacks had appeared and the patient felt well showing no signs of cardiac decompensation

Case 4 ♀ born 1914 In 1960 headache appeared and hypertension was diagnosed blood pressure 195/105 Since 1962 angina pectoris In 1963 anterolateral myocardial infarction commenced with a fainting attack *Coronary T* waves developed and there was a pathological rise in transaminases Syncope appeared after this and vertigo varying from once a day to once *a month* No ECG was recorded and the pulse was not palpated during an attack but the patient noticed that the heart beat slowly during the attacks No murmurs

position with a bicycle ergometer. Pressures and ECG were recorded after 1, 2, 4, 6 and 8 minutes of exercise. CO determinations and arterial blood sampling for the determination of pH, oxygen (PaO_2) and carbon dioxide ($PaCO_2$) tension, standard bicarbonate and lactate were done according to the schedule described in chapter V for the exercise test. The load was 300 kpm/min for men except in case 1 for which it was 150 kpm/min and 200 kpm/min for women. Ten minutes after the end of the exercise digoxin (Lanoxin® B & W) in a dosage of 1 mg/70 kg body weight was injected intravenously during 10 minutes after which the double lumen catheter was withdrawn from the wedge position. Pressures and ECG were recorded every ten minutes and one hour after the end of injection the tip of the double lumen catheter was again manipulated into the wedge position, a new CO determination was done and the exercise procedure was repeated.

The *pulmonary vascular resistance* (PVR) expressed in dyn sec cm^{-5} was calculated as the difference between the mean pulmonary artery ($\bar{P}_{PA}$) and pulmonary capillary venous ($\bar{P}_{PCV}$) pressures in mm Hg divided by the cardiac output in ml/sec and multiplied by 1332 (2).

The *left ventricular minute work index* in kilogrammeters per minute per square meter body surface area (kgm/min/sq m BSA) was calculated according to the following formula

$$\frac{CI \times (\bar{P}_{AO} - \bar{P}_{PCV}) \times 13.6}{1000}$$

where CI is the cardiac index, $\bar{P}_{AO}$ the mean aortic pressure and $\bar{P}_{PCV}$ the mean PCV pressure. The *left ventricular stroke work index* in grammeters/sq m BSA was calculated according to the formula

$$\frac{SI \times (\bar{P}_{AO} - \bar{P}_{PCV}) \times 13.6}{1000}$$

where SI is the stroke index. The *right ventricular minute work index* and *right ventricular stroke work index* were calculated similarly but the mean pulmonary and the mean right atrial pressures were used instead of $\bar{P}_{AO}$ and $\bar{P}_{PCV}$, respectively.

Apart from nausea and vertigo after catheterization in one patient, probably as a result of digitalis intoxication, no *complications* appeared.

The hemodynamic response to digitalis was studied in five patients with a pacemaker* implanted at least three months before the catheterization. Digitalis, if given, was withdrawn in time to render the patients free of its influence at catheterization.

Case 1. ♂ born 1893. Cerebral concussion in 1946. In 1958 a left sided hemiplegia occurred with good but not complete regress. Blood pressure was 230/110. Luetic reaction and TPI test in blood were positive. Penicillin was given and the Wassermann reaction became negative. In August 1964 he experienced a period with three syncopal attacks. Afterwards irregular heart activity was noted but no fainting. In November 1964 there were further syncopal attacks. ECG showed complete heart block (CHB) and right bundle branch block

* Manufactured by Medtronic Inc., Minneapolis, Minn., USA

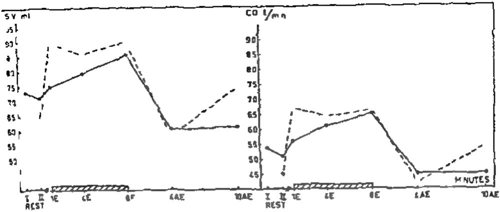


Fig 34 Stroke volume (SV) and cardiac output (CO) before ——— and after - - - - Lanoxin Symbols as in fig 33

In two patients cases 1 and 4 the *ventricular rate* rose because of extra systoles during exercise The rise was somewhat more pronounced before than after digitalis administration These two patients showed the least cardiac functional capacity clinically their pulmonary capillary venous (PCV) pressure was higher than in the three other patients despite a lower cardiac index (CI) (for details see the Appendix table I)

After digitalis administration the *cardiac output* (CO) was slightly lower at rest as shown in fig 34 but this difference was to a large extent ascribable to case 2 with values of 5 1 and 3 2 l/min before and after digitalis administration respectively CO was increased after one minute's exercise following digitalis administration but this difference decreased later during exercise The *stroke volume* (SV) followed the same pattern (fig 34)

The *systolic aortic blood pressure* at rest was slightly lower after digitalis administration while the reverse pattern was seen during exercise as shown in fig 35 The means for the *diastolic pressure* and the *mean aortic pressure* ($\bar{P}_{AO}$) showed a similar tendency but in analysis of table I in the

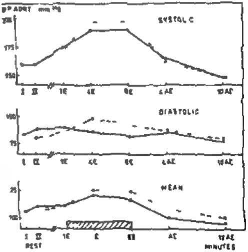


Fig 35 Aortic blood pressure before ——— and after - - - - Lanoxin Symbols as in fig 33

were auscultated at a heart rate of 66/min and blood pressure of 125/80 mm Hg. Hgb 12.8 g %. ECG at rest showed a sinus bradycardia and A-V nodal and ventricular premature beats. Heart volume was 640/400 ml/sq.m BSA. A pacemaker was implanted in April 1965. Postoperatively a left pleural exudate appeared and was evacuated. The attacks of syncope and vertigo disappeared and the patient felt well nine months after operation although she became abnormally dyspneic on exertion. She had a roentgenologically verified gallstone. Postoperative spirometry was normal except a slight increase of residual volume (RV) and FRC.

Case 5 ♀ *born 1895*. Earlier history was noncontributory. In January 1965 a few syncopal attacks occurred. She was said to have an elevated blood pressure (systolic around 200 mm Hg). During the spring of 1965 she noted a slow pulse. There were no signs of cardiac decompensation and she had no angina pectoris. A systolic murmur grade 3 was heard in the 3rd left intercostal space at a pulse rate of 33 beats/min and a blood pressure of 150/65. Hgb 14.2 g %. ECG showed CHB and right bundle branch block type. The heart volume was 900/515 ml/sq.m BSA with a left ventricular enlargement. More syncopal attacks appeared and a pacemaker was implanted in July 1965. Postoperatively there was a thrombophlebitis in the right leg and left pleural exudation. She was discharged in good condition and without syncopal attacks. Postoperative spirometry showed a slightly decreased $FEV_{1.0}$, VC and TLC 75 % of normal and MVV_F 64 % of normal while RV and FRC were normal. Six months after operation the patient was in a good condition with no clinical signs of cardiac decompensation.

B. Results

Individual observations and mean for the different parameters are given in the Appendix, table E. Repeated ECG and pressure recordings after the catheters had been inserted showed that the patients had reached a steady state before the resting values were measured. This is also indicated by the absence of a difference between the two resting values thirty and forty minutes after introduction of the catheters. The reproducibility of the methods and the occurrence of the basal state in the patients have been discussed in chapter VI.

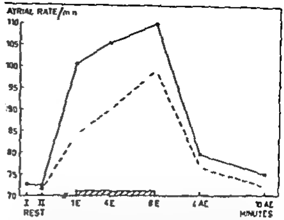


Fig. 33. Atrial rate in 5 patients with an artificial pacemaker before ——— and after - - - i.v. administration of 1 mg Lanoxin/70 kg b.w. The figure shows the mean values obtained at rest (I and II), during exercise E and after exercise AE. 1E denotes values obtained at 1 minute of exercise, 4AE values obtained at 4 minutes after exercise. //////// denotes exercise.

The *atrial rate* (fig. 33) at rest was mainly unchanged after digitalis administration. During exercise, however, there was a striking difference, with lower values after digitalis. There was a marked fall four minutes after exercise and a further fall to preexercise level ten minutes after the end of exercise in both groups.

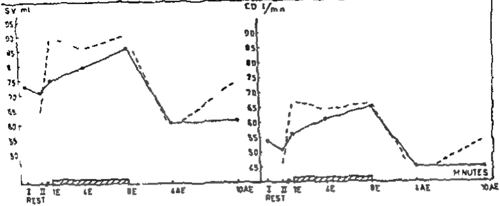


Fig 34 Stroke volume (SV) and cardiac output (CO) before —— and after Lanoxin. Symbols as in fig 33

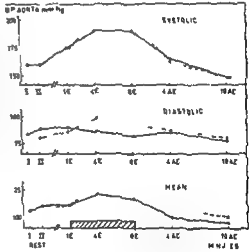


Fig 35 Aortic blood pressure before —— and after Lanoxin. Symbols as in fig 33

In two patients (cases 1 and 4) the *ventricular rate* rose because of extrasystoles during exercise. The rise was somewhat more pronounced before than after digitalis administration. These two patients showed the least cardiac functional capacity clinically, their pulmonary capillary venous (PCV) pressure was higher than in the three other patients despite a lower cardiac index (CI) (for details see the Appendix, table F).

After digitalis administration the *cardiac output* (CO) was slightly lower at rest as shown in fig 34 but this difference was to a large extent ascribable to case [illegible] with values of 5 1 and 3 2 l/min before and after digitalis administration respectively. CO was increased after one minute's exercise following digitalis administration but this difference decreased later during exercise. The *stroke volume* (SV) followed the same pattern (fig 34).

The *systolic aortic blood pressure* at rest was slightly lower after digitalis administration while the reverse pattern was seen during exercise as shown in fig 35. The means for the *diastolic pressure* and the *mean aortic pressure* ($\bar{P}_{AO}$) showed a similar tendency but an analysis of table E in the

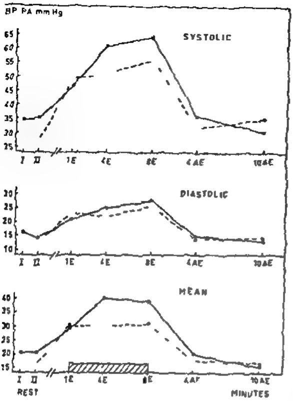


Fig 36 Pulmonary blood pressure (PA) before ——— and after - - - Lanoxin Symbols as in fig 33

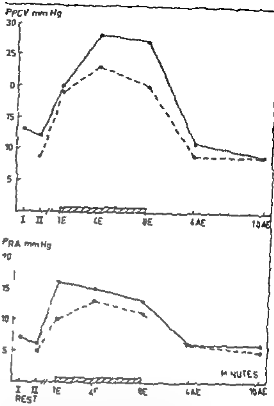


Fig 37 Mean PCV pressure ($\bar{P}_{PCV}$) and mean right atrial pressure ($\bar{P}_{RA}$) before ——— and after - - - Lanoxin Symbols as in fig 33

Appendix shows that the individual variations were great

The *systolic pulmonary artery blood pressure* fell already at rest after digitalis administration (fig 36) After one minute's exercise the values after digitalis were slightly higher than before digitalis but later during exercise there was again a fall to below the predigitalis level A similar pattern was observed for the *diastolic* and *mean pulmonary artery pressure* ($\bar{P}_{PA}$)

The *PCV mean pressure* ($\bar{P}_{PCV}$) was normal at rest in two patients, increased in two and in one a borderline value was recorded Fig 37 shows a decrease of $\bar{P}_{PCV}$ already at rest after digitalis administration An equalization occurred after one minute's exercise but later during exercise a fall again appeared Unfortunately no satisfactory PCV pressure curve could be obtained in one patient (case 5) after digitalis administration but the above pattern occurred in all the recordings which could be used even when the PCV pressure at rest was normal or borderline The *mean right atrial* (P_{RA}) *pressure* (fig 37) was also lower during exercise after digitalis administration but the difference was most pronounced after one minute's exercise while the difference in the resting values was but slight

C Discussion

Since only a few patients were available for studies of the type presented in this chapter it was not feasible to use some as controls in all cases however pressure and flow recordings were repeatedly checked after the introduction of catheters and the values showed that the patients were in a steady state at the beginning of the first exercise

The circulatory effects of repeated exercise have been investigated by Widimsky et al (13a) who studied four healthy volunteers and four patients with lung disease they found significant changes only in the $\bar{P}_{PA}$ which was lower both at rest and during exercise forty five minutes after the initial exercise period Malmborg (91) using a patient material and time intervals more similar to those in the present study observed in his nine patients a probably significant ($P<0.05$) fall in $\bar{P}_{PA}$ of 0 8 mm Hg at the second exercise In both these materials the decrease in $\bar{P}_{PA}$ was much less than that found in the present study No significant changes were found by Malmborg (91) and Widimsky et al (13a) in other comparable parameters One is therefore justified in attributing most of the changes obtained at the second exercise to the digitalis administration

The recent literature on the effect of acute digitalization on the hemodynamics at rest and exercise has been discussed by Malmborg (91) In *healthy subjects or patients with non failing hearts* no or slight changes appear in CO SV and pressures in the lesser circulation Granath et al (50) also observed no effect of acute digitalization on the hemodynamics either at rest or during exercise in six healthy elderly men In a recent review on the cardiocirculatory actions of digitalis Braunwald et al (17) stated that with refined technique it can be shown that digitalis exerts an effect on the non failing heart too the right ventricular contractile force increased after digitalis administration as did the maximum rate of intraventricular pressure rise during isometric ventricular contraction

In *patients with heart failure* the beneficial effect of digitalis is well established It consists of an increase in resting CO lowering of the heart rate increase of SV and lowering of the intracardiac and pulmonary artery pressures (39 80 114)

The *results in the present study* showed that digitalis had pronounced effects on the hemodynamics in spite of a constant ventricular rate The pattern was similar for the two patients in whom extrasystolies appeared during exercise The number of extrasystolies appeared to decrease in these two patients at the second exercise and there were no serious arrhythmias which might be caused by the lowering effect of digitalis on the ventricular fibrillation threshold as found by Grondin et al (5a) in dogs with competing rhythms given very large doses of lanatoside C

Benchimol et al (7) investigated the effect of 1 mg strophantin G given intravenously to six patients with an

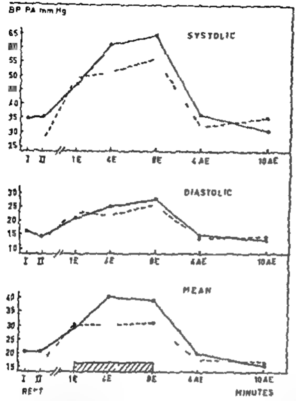
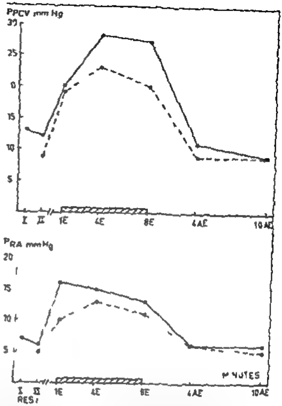


Fig 36 Pulmonary blood pressure (PA) before ——— and after - - - - Lanoxin Symbols as in fig 33



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The recent literature on the effect of acute digitalization on the hemodynamics at rest and exercise has been discussed by Malmborg (91) In *healthy subjects or patients with non failing hearts* no or slight changes appear in CO SV and pressures in the lesser circulation Granath et al (50) also observed no effect of acute digitalization on the hemodynamics either at rest or during exercise in six healthy elderly men In a recent review on the cardiocirculatory actions of digitalis Braunwald et al (17) stated that with refined technique it can be shown that digitalis exerts an effect on the non failing heart, too the right ventricular contractile force increased after digitalis administration as did the maximum rate of intraventricular pressure rise during isometric ventricular contraction

In *patients with heart failure* the beneficial effect of digitalis is well established It consists of an increase in resting CO lowering of the heart rate increase of SV and lowering of the intracardiac and pulmonary artery pressures (39 80 114)

The *results in the present study* showed that digitalis had pronounced effects on the hemodynamics in spite of a constant ventricular rate The pattern was similar for the two patients in whom extrasystoles appeared during exercise The number of extrasystoles appeared to decrease in these two patients at the second exercise and there were no serious arrhythmias which might be caused by the lowering effect of digitalis on the ventricular *fibrillation threshold* as found by Grondin et al (55) in dogs with competing rhythms given very large doses of lanatoside C

Benchimol et al (7) investigated the effect of 1 mg strophantin G given intravenously to six patients with an

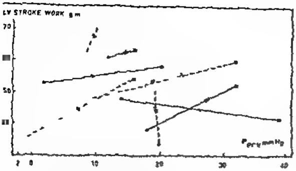

Fig 38 Left ventricular stroke work/sq m BSA in relation to mean PCV pressure ($\bar{P}_{PCV}$) before ——— and after Lanoxin ● =rest ■=*exercise The small perpendicular lines refer to the case numbers in chapter IX*

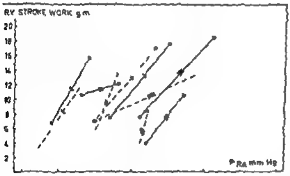

Fig 39 Right ventricular stroke work/sq m BSA in relation to mean right atrial pressure ($\bar{P}_{RA}$) before ——— and after Lanoxin ● =*rest* ■=*exercise See further legend to fig 38*

artificial pacemaker No intracardiac pressures were recorded and *the patients did not perform any exercise* These authors observed a moderate increase in CI SI and stroke power in the absence of any *change in the ventricular or atrial rates The arterial* pressure did not change significantly after digitalization

It is known that *digitalis* exerts both *cardiac* and extracardiac *effects* (104) The direct effect of digitalis on the heart is also evident in the present series An *analysis of fig 38 shows that* digitalis usually lowered the filling pressure of the *left* ventricle, as reflected by the $\bar{P}_{PCV}$ at unchanged or increased levels of stroke work The result was less *striking for the right* ventricle *(fig 39)*

McMichael and Sharpy Schafer (94) suggested that digitalis exerts an *extracardiac effect* in relaxing the veins which results in a venous pooling Werkö et al (134) concluded that lanatoside C has a direct effect on the renal *circulation* and *sodium* excretion It is interesting in this connection that when Withering made his original discovery of the effect of the foxglove in patients with edema, the drug was considered to have a purely diuretic action

With respect to the extracardiac *effects of digitalis it is noteworthy that the filling pressures of the right and* left ventricles showed a different response in the present *series* After one minute s exercise the filling *pressure* of the right ventricle *as mirrored in the $\bar{P}_{RA}$ was lower after digitalis than* before while $\bar{P}_{PCV}$ was very little influenced by digitalis After eight *minutes exercise on the other hand the reverse was found (fig 37)* This may be connected with the changes *in central* blood volume (CBV) At the *beginning of exercise* CBV was higher *after digitalis than before* while this *pattern was not uniform* at the end of exercise (individual observations are given in the Appendix table I) McMichael and Sharpy Schafer (94) suggested a direct relaxant effect on the

veins as the primary action of digitalis and hence a venous pooling. This mechanism is also indicated by the findings of Braunwald et al (17) but they believed that the observed venodilatation was probably mediated indirectly. If digitalis exerts its main effect on the veins with a venous pooling as a result the beneficial effect should diminish during prolonged exercise.

There was no consistent effect on the arterial oxygen tension at rest or during exercise and no change in arterial pH at rest after digitalis administration. After eight minutes exercise however pH fell from 7.42 to 7.40 before digitalis but remained at 7.42 after digitalis administration (individual observations are given in the Appendix table E). This was probably produced at least in part by the increase of arterial lactate concentration which at rest was uninfluenced by digitalis but during exercise and to a decreasing degree also after exercise showed consistently higher values before than after digitalization. This result may well be explained at least in part by the improved circulation reflected in a CO and SV rise after digitalis but there was no obvious correlation between the difference in lactate concentration and the improvement indicated by a plot of PCV against left ventricular work (fig 38) or the CO rise. It is possible that some patients are able to open new metabolic pathways and thus utilize anaerobic energy the amount of which is not directly measurable from the lactate concentration values.

Summarizing the acute circulatory effects of digitalis administration have been studied in five patients at rest and during exercise at least three months after the implantation of an artificial pacemaker. The effect of digitalis consisted of a marked decrease of the atrial rate, a decrease of the PA pressures and of $\bar{P}_{PCV}$ at rest and during the later phase of exercise and a decreased $\bar{P}_{RA}$ especially in the first phase of exercise. CO and SV were higher during exercise after digitalis administration while the arterial lactate concentration decreased. The beneficial effect of digitalis and the absence of serious arrhythmias after digitalis in these patients motivate the administration of digitalis to patients with an artificial pacemaker if they show symptoms of cardiac decompensation.

Concluding remarks

There are publications on symptomless patients with a history of complete heart block (CHB) for many years. Benjamin and White (9) described two cases with CHB of more than 35 years duration verified electrocardiographically, while in the present material there was one patient who lived 18 years after CHB had been electrocardiographically verified. The longest period of CHB documented by the electrocardiogram (ECG) was 21 years in the material of Penton et al (102). It is apparent then that CHB can carry a good prognosis and may even be turned to good account—Hyman (62) described a 57 year old man with CHB who always managed to obtain sick leave from school by having his teacher count his pulse rate! As a rule, however, the prognosis is very unfavorable as shown in chapter IV; half the patients died less than one year after the electrocardiographic verification of CHB. No reliable prognostic features were found when analyzing different parameters such as the blood pressure, X-ray of the heart, ECG and various clinical symptoms. Not even a satisfactory circulatory response to exercise (case 19 in the Appendix, table 4) was a guarantee for a good prognosis, as shown in chapter VII, and the response to atropine was not helpful, as shown in chapter VIII. The prognostic difficulties have been stressed in the literature (40, 96, 138, 142) and despite a great arsenal of therapeutic remedies and methods, some more sophisticated than others [see Glenn (48)], it is felt that the increasingly frequent use of cardiac pacemakers is warranted (4). This concept is further supported by the finding in the Malmö material that there was no difference in one-year survival between patients who had or had not received medical treatment such as atropine, ephedrine or isopropylnoradrenaline or a combination of these.

The general availability of artificial pacemakers thus represented a major advance. A survey is given by Furman (42). The two most common ways of implanting an artificial pacemaker is through the external jugular vein, which is performed in local anesthesia, and through a thoracotomy under general anesthesia. Neither of these approaches can be regarded as a major operation, as witness the comparatively low operative mortality figures. In a recent paper Lagergren et al (78) reviewed 305 patients operated with the jugularis approach. The longest

follow up time was three and a half years The number of deaths was highest during the first six months Thirty eight patients or 12 % died within this period and forty eight, or 16 % died in the total material The mode of death was most often sudden unexplained death and intercurrent disease Chardack et al (27) reported nine postoperative deaths in 100 patients who were given an artificial pacemaker 81 % of them through a thoracotomy For fifty of these patients the one year survival was about 80 % In the Malmö material (128) forty eight patients were operated with a thoracotomy and a pacemaker of the Medtronic type was implanted in thirty six of these with a follow up time of six months or more six patients (17 %) died within this time four of them having an acute myocardial infarction one had pulmonary emboli and one died five weeks post operatively in a progressive cardiac decompensation No further deaths occurred in patients having a follow up time of one year Nine patients (19 %) died in the total material The longest follow up time was four and a half years In all these materials the indications for operation have been both CHB and Adams Stokes attacks but as shown earlier (63) the one year survival is as bad in patients with Adams Stokes attacks as in patients with CHB half of the patients being dead one year after diagnosis

The above figures indicate that the prognosis in patients with CHB is improved with artificial pacemaker treatment but that operation is accompanied by a certain mortality consequently it would therefore be advantageous to be able to prognosticate in the individual case As shown in chapter IX some signs were of value for the prognosis for the material as a whole but no completely reliable prognostic sign was found in the individual cases This is the main argument for having very wide indications for artificial pacing in patients with CHB—as is the case in patients with Adams Stokes attacks

There are other indications too As was discussed in the introduction to chapter VII the *cardiac output* (CO) rises at least to a certain level in patients with CHB when the heart rate is increased by an artificial pacemaker The P wave cardiac stimulator by which the ventricles are paced synchronously in relation to the atrial activity is reported to constitute a further improvement [for discussion see Glenn (48)] Bostroem et al (15) obtained a mean CO of 4 22 l/min when a patient with CHB at *operation* received a P wave synchronized artificial stimulation but only 2 05 l/min when the stimuli were not synchronized These authors also found that synchronized pacing overcame the frequent occurrence of very *high right* atrial pressure waves produced by right atrial contraction against closed tricuspid valves a phenomenon that was also frequently found in the present study both in patients with CHB and in patients with an artificial pacemaker This finding was early demonstrated by Lagerlöf and Werkö (79) Samet et al (108) comparing the

Table 18 *Physical working capacity in kpm/min in 5 male patients before and after pacemaker implantation The figures refer to the case numbers in the Appendix, table 4*

Case No	Before pacemaker implantation	After pacemaker implantation
3	300	300
7	300	375
9	3.0	600
10	3.0	400
14	300	600
Mean	320	4.5

hemodynamic effects of atrial and ventricular pacing at rates above the intrinsic one in patients with sinus rhythm reported a decrement in CO and in systemic arterial pressure together with atrioventricular regurgitation in ventricular pacing and Benchimol et al (8) also comparing the effects of atrial and ventricular pacing in patients with sinus rhythm concluded that atrial systole significantly improved cardiac function in patients with heart disease whereas it had little hemodynamic effect in normal subjects Kaiser et al (73) measured the oxygen consumption (VO_2) at rest and during exercise in patients with P wave synchronized and nonsynchronized artificial pacing they obtained a higher VO_2 in patients with synchronized pacing if the myocardium was not too damaged Their indications for the synchronized pacemaker were patients with interference between the pacemaker and idioventricular rhythm and comparatively young patients who could be expected to return to work

Five patients in the Malmo material were exercised in the sitting position on a bicycle ergometer before and after implantation of an artificial pacemaker with a thoracotomy The working capacity (calculated as described for the precatheterization exercise test in chapter II) increased after pacemaker implantation in four of the five cases, with a mean increase from 320 to 455 kpm/min (table 18) The most pronounced rise was observed in case 14 (Appendix, table 4) which showed the lowest ventricular rate during CHB

The *renal function* is impaired in patients with CHB Schuller et al (110) showed that the renal flow and glomerulus filtration rate, reflected in PAH and inulin clearance were markedly decreased and rose after pacemaker implantation as did the renal fraction of CO In some cases the serum creatinine level was increased an artificial increase of the ventricular rate resulting in a fall of creatinine

Cerebral symptoms excluding syncopal attacks are not uncommon in CHB (141) and these symptoms have been reported to disappear or decrease in intensity after pacemaker implantation (32) Schuller et al (111) showed an improvement of the electroencephalogram and of psychological tests specially designed to measure cerebral lesions

Peripheral arterial insufficiency caused by a low CO has been studied by Edhag and Zetterquist (33) who exercised patients in the recumbent

Table 19 Occurrence of sudden death outside and in hospital in patients with constant and transient complete heart block (CHB) Figures in brackets denote the number of patients with a history of syncope The table refers to the whole material of 204 patients A means that death was a sudden death B that it was not

	Constant CHB				Transient CHB			
	Dead in hospital		Dead outside hospital		Dead in hospital		Dead outside hospital	
	A	B	A	B	A	B	A	B
No of patients	39 (34)	54 (29)	5 (3)	3 (1)	4 (3)	32 (11)	1 (1)	9 (3)
% of total	26.5	36.7	3.4	2.1	2.7	21.8	0.7	6.1

position at different pulse rates They found that the patients could perform a higher exercise at the higher pulse rate but that the lactate concentration remained unchanged

There are thus many factors in favor of wide indications for pacemaker implantation in patients with CHB

Problems of another nature also emerge when considering patients with CHB Should for example such a patient be allowed to have a driver's licence? To illustrate this problem a study was made of the mode of death and the place where death occurred It is apparent from table 19 that most of the patients with CHB died in hospital Only six out of 147 (five with constant and one with transient CHB) died a sudden death outside hospital There is then a certain but no great risk of sudden death outside hospital in patients with CHB The figures in brackets in table 19 show the patients with a known history of syncope Excluding these only two patients out of 147 died suddenly outside hospital

A survey of the literature indicates that CHB is usually ascribed to atherosclerotic heart disease As shown in chapter III a large group in the present material displayed no signs of ischemic heart disease This was verified by autopsy in two thirds of the deceased patients and a coronary arteriography showed only minute irregularities in the coronary arteries in a patient not belonging to the material but considered to have CHB of unknown etiology The case for differentiating between patients with CHB of unknown etiology and patients with CHB produced by nonacute coronary heart disease is supported by the microscopical findings of Lenègre (83) and the clinical reports of Zoob and Smith (143) and Moreau et al (99) In the present material the two groups displayed differences in various parameters Compared with the group with unknown etiology the nonacute coronary heart disease group was characterized by a lower frequency of changes of bundle branch block type (0.05>P>0.01) a lower frequency of syncopal attacks (0.05>P>0.01) and a higher mean ventricular rate (0.05>P>0.01) Moreover the coronary

heart disease group showed a lower one year survival rate, a higher mean age, a higher percentage of male patients and a lower percentage of positive Erlanger-Blackman phenomenon, but these differences were not significant.

It is noteworthy that no case of congenital CHB was found in the present material during 1951—1964. Subsequently, however, CHB has been diagnosed in a newborn. A slow heart rate was diagnosed in the fetus when the mother was admitted for delivery. Caesarean section was therefore performed. At a check up one month before delivery the fetal heart sounds were reported to be normal. The baby was given isopropylnoradrenaline to increase the pulse rate and to counteract possible Adams Stokes attacks and she was well two months after delivery with persisting CHB.

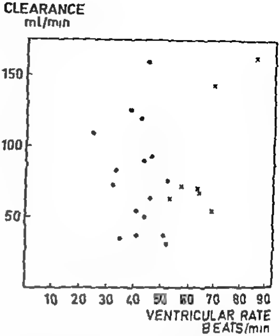

Fig. 40. Creatinine clearance in relation to ventricular rate at follow up examination.
● =patients with complete heart block (constant CHB)
X=patients without complete heart block (transient CHB)

The period immediately after the onset of CHB seems to be the most critical not only as far as the mortality is concerned but also because many symptoms are most pronounced during this time. Later there seems to be an adaptation to the slow ventricular rate. As shown in chapter III the functional capacity improved and the intensity of orthostatic reactions decreased when the results at follow up were compared with those obtained just after the onset of CHB, but pre CHB levels were not reached. The kidneys may follow the same pattern and be capable of further improvement long after the onset of CHB: thus in one of the patients reported by Schuller et al (111) a distinct improvement in the renal function was obtained despite a CHB of 18 years standing before operation. In the present material the findings for creatinine clearance showed a wide range (individual observations are given in the Appendix, table A). No correlation to the ventricular rate was obtained (fig. 40). One possible explanation may be that during the determination of creatinine clearance the ventricular rate was too high to impair the renal function significantly. The critical rate at which renal impairment occurs may vary widely from subject to subject, which is the case for the stroke volume (SV) as was pointed out by McGregor and Klassen (92).

The nature of this adaptation proc

ess is not known However it probably takes some time for the SV to rise to the high values obtained in well established CHB and reported in the hemodynamic part of this study Even if CHB is possibly better tolerated in humans than in dogs (120) it may be appropriate to refer to the results of acute CHB in dogs Starzl et al (119 120) reported an immediate deterioration just after surgically induced CHB but subsequently there was a gradual improvement not only in SV but also in CO and exercise tolerance

Summarizing all these factors it may be concluded that the one year survival in patients with CHB is about 50 % and that in materials treated with an artificial pacemaker it is considerably higher Since no reliable prognostic factors were found it seems that *the indications for pacemaker treatment in patients with CHB should be very wide* This approach may not be applicable to patients with CHB produced by digitalis intoxication since death was not usually caused by the intoxication but by the heart disease for which digitalis was administered Furthermore there are reports which indicate that artificial pacing was of no value in reducing the high mortality in patients with acute myocardial infarction complicated with CHB On the other hand more optimistic reports have also been published and a definitive answer has yet to be found

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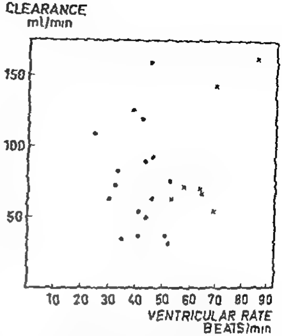

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previous history showed that gall bladder disease was common. Excluding the group where acute myocardial infarction produced CHB, no cases of *myocardial infarction* were observed after CHB had been established, while seven patients got a diagnosis of *cerebral lesion*.

The 55 *living patients* were studied at the *follow up examination*. In this selected material *angina pectoris* was infrequent while *cardiac decompensation* was found in 22 %. The *functional capacity* was reduced after the onset of CHB but improved later, although preCHB levels were not reached. The frequency and intensity of orthostatic *reactions* increased just after the beginning of CHB but a subsequent improvement was observed.

The *electrocardiographic findings* in the 204 patients gave an average atrial rate of 91.8 beats/min and a ventricular rate of 43.0 beats/min. *Atrial fibrillation* was found in 19 and *atrial flutter* in 2 of the 204 patients. The *Erlanger Blackman phenomenon* was common and more frequent in patients with unknown etiology than in patients with ischemic heart disease. *AV block* of the first and second degree was common both before CHB and after CHB had disappeared, as was *bundle branch block*, especially right sided. CHB was accompanied by an increase in systolic *blood pressure* and pulse pressure while the diastolic pressure was decreased. No correlation was found between pulse rate and blood pressure in the total material while the pulse pressure was higher in the older patients than in the younger.

Chapter IV deals with *prognostic aspects* in the 193 patients in whom CHB was diagnosed during 1951—1964. This material is presented in table 10. Fig. 8 shows the *survivorship curves* for the total material and the different etiological groups as well as for the total population of Sweden. Half of the patients in the total material died less than a year after diagnosis. The highest mortality was found in patients with acute myocardial infarction especially when it was situated anteriorly and the lowest mortality in patients with rheumatic heart disease. In half of the patients with *acute myocardial infarction* CHB appeared 24 hours or less after the infarction. The duration of CHB was usually only a few days in these patients. Persisting CHB after an acute myocardial infarction is very uncommon. The infarction was usually situated posteriorly. CHB including Adams Stokes attacks was the *cause of death in one third of the* patients. The occurrence of *syncope* or *Adams Stokes* attacks in patients with CHB seemed to make the one year survival rate more unfavorable but the differences were not striking. Several *electrocardiographic features* were analyzed from a prognostic point of view. No reliable prognostic signs were found, although a positive *Erlanger Blackman* phenomenon seemed to be favorable. Bundle branch block type seemed to worsen the prognosis in patients with acute *myocardial* infarction and coronary heart disease, while this was not the case in patients with CHB of unknown etiology. Constant CHB implied a lower one year survival

Summary

The first part of this book is devoted to a clinical and prognostic study of complete heart block (CHB) in Malmö. In the second part the hemodynamic reaction to an orthostatic test, to exercise and to atropine is analyzed in a selected material of CHB patients. Finally the hemodynamic effects of digitalis at rest and during exercise were investigated in five patients with an artificial pacemaker.

Malmö, which has a quarter of a million inhabitants, is unusually suitable for studies on the frequency and natural history of CHB since the whole town is served by a single hospital. It is therefore very probable that the 204 patients found at a perusal of the electrocardiographic files of the Heart Laboratory, Malmö General Hospital comprise almost all of the patients in Malmö known to have CHB. These 204 patients were used for the clinical study. For reasons explained in chapter IV only 193 patients were used for the prognostic study. The material is presented in fig 1.

Chapter II deals with the *criteria* used for the diagnosis of CHB and the *material* and *methods* used for the *clinical* and *prognostic study*.

Chapter III contains an analysis of the *clinical aspects of CHB*. The *incidence* was calculated to 6.3 patients per *100 000 inhabitants per year*. The patients were *classified* in seven groups *according to the dominant disease producing CHB*: unknown etiology, acute myocardial infarction, nonacute coronary heart disease, hypertension, rheumatic heart disease, digitalis intoxication and finally a miscellaneous group. The material is presented in table 1. Various etiological aspects are discussed. The reasons for placing as many as one third of the patients in the group with unknown etiology are presented. From a comparison of the frequency of *diphtheria* with the frequency of patients with CHB of unknown etiology it was concluded that diphtheria is not a common cause of CHB in this group. Most of the CHBs were diagnosed in patients in the *age group 70—79 years* but nine per cent of the patients were younger than 50 years at discovery. The *sex distribution* showed a male preponderance except in the hypertensive and digitalis *intoxication groups*. Only in nine patients was the *cause of consultation* the slow pulse rate while in one fourth it was syncope and in half the material other cardiac symptoms. The

slightly The degree of increase of ventricular rate after atropine cannot be used as a *prognostic* sign

Chapter IX presents the circulatory effects of acute *digitalis* administration (1 mg digoxin/70 kg body weight) at rest and during exercise in patients with an artificial pacemaker Digitalis produced a marked decrease of the atrial rate during exercise as well as a decrease of the pulmonary artery pressures and of the mean PCV pressure at rest and during the later phase of exercise The mean right atrial pressure also decreased most markedly in the first phase of exercise Cardiac output and stroke volume were higher during exercise after digitalis administration and the arterial lactate concentration was lower These effects motivate the administration of digitalis to patients with an artificial pacemaker if the patients show symptoms of cardiac decompensation

In chapter X the unfavorable prognosis *in patients with CHB despite* medical treatment is contrasted with the better survival rate in patients with CHB and Adams Stokes attacks treated with an artificial pacemaker It is concluded that the *indications for artificial pacemaker implantation* should be very wide since the prognosis in these patients is bad and there are no reliable prognostic signs

The physical working capacity was improved after the pulse rate had been raised with an artificial pacemaker and literature is quoted to show that the renal and cerebral functions were improved and the peripheral blood flow increased during artificial pacing

The question is discussed of whether CHB patients should be allowed to have a driver s licence In only six patients out of 147 was death outside hospital a sudden death and four of these had a known history of syncope

The main *differences between CHB of unknown etiology* and CHB produced by *nonacute coronary heart disease* are reviewed a newborn with *congenital CHB* is presented and the possibility of an adaptation to the slow ventricular rate in patients with CHB is discussed

To *sum up* the summary a prognostic study of patients with complete heart block (CHB) has shown that the prognosis is bad half of the patients being dead within one year There are *no reliable* prognostic signs and consequently the indications for artificial pacemaker implantation should be wide in these patients There are indications for the administration of digitalis to patients with an artificial pacemaker who show signs of cardiac decompensation

rate than transient CHB The prognosis could not be predicted accurately in individual cases from the *blood pressure* values or the *X-ray* findings

Chapter V describes the *material* (also presented in fig 1) and *methods* used *for the hemodynamic studies* Group B comprises the patients with CHB at *catheterization and group T those* who had previously had a CHB but had sinus rhythm at catheterization *Resting values* obtained thirty and forty minutes after the catheters had been introduced showed a good reproducibility and their level indicated that the patients were in a basal state

An *orthostatic test* was made by tilting the patients 53° keeping them in this position for ten minutes then performing an *exercise test* with maximal loads in the supine position and thirty minutes after this was finished an *atropine test*

Chapter VI presents the results of the *orthostatic test* Patients with CHB at catheterization (group B) showed a slight increase of atrial and ventricular rate in the standing position, while cardiac *output* and *stroke volume* decreased, as did the aortic systolic blood pressure pulse pressure and mean pressure while the diastolic blood pressure showed a slight increase The mean right atrial pressure fell in both group B and T (which comprised the patients who had had a CHB but showed sinus rhythm at catheterization) but in group T the drop to the lower level occurred earlier The peripheral resistance rose in both groups Fewer orthostatic reactions appeared in the patients with CHB than in those with sinus rhythm

Chapter VII presents the results of the *exercise test* A physical exercise test in both the *sitting* and the supine *position* showed a decreased working capacity in patients with CHB During exercise *in the supine position* the atrial rate rose markedly The ventricular rate rose too, but less so Cardiac output was low at rest but *increased during exercise*, since both the ventricular rate and the stroke volume increased The *oxygen consumption* was more than tripled and the arteriovenous oxygen difference more than doubled during exercise despite a high resting value Both arterial pH and standard bicarbonate decreased during exercise but pH was normalized earlier after exercise The lactate concentration curve showed a peak at the end of exercise

A *comparison with* values obtained by Granath et al (30) in *healthy old men* showed a decreased physical exercise capacity in the CHB patients The type of response to exercise in a patient with CHB was of no value for the *prognosis quo ad vitam*

Chapter VIII gives the results of the *atropine test* Atropine sulfate (0 1 mg/10 kg body weight) given intravenously to patients with CHB produced an increase of the atrial rate and usually of the ventricular rate as well though the latter was less pronounced Cardiac output remained unchanged The aortic systolic blood pressure fell

Appendix

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The preparation of this work was greatly aided by the interest, enthusiasm and constructive criticism of Professor Jan Waldenström. I am also indebted to Professor Waldenström for placing material and personnel resources of the Heart Laboratory, Medical Department, at my disposal.

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Bundle branch block type: Right	Bundle branch block type: Left	Atrial rate at rest in beats min	Ventricular rate at rest in beats min	Blood pressure in mm Hg	Creatinine s in mg per 100 ml	Clearance in ml/min/1 73 sq m BSA	Hgb in g per 100 ml	Urine: Prot	Urine: Gluc	Spirometric data in ATPS: VC l	VC % pred	FEV1.0 l	FEV1.0 % pred	FEV %	FEV % % pred
		86	44	190 100—90	0.37	159	11.4	0	0	3.80	98	3.03	128	80	125
+		100	52	190 90—80	1.66	31	12.9	(±)	0	[illegible]	87	1.60	82	56	85
+	+	60	30	185 80—70	1.12	63	13.9	0	0	3.73	91	2.43	96	66	103
+		100	40	160 80—65	1.05	61	13.3	+	0	2.40	60	1.75	70	73	112
		108	43	260 90—80	0.67	90	12.3	(−)	0	3.03	81	2.05	89	68	105
		a fibr	51	175 110—90	0.76	57	16.1	0	0	2.15	53	1.80	62	73	112
+		63	32	175 85—70	1.09	73	15.0	0	0	3.95	105	3.05	129	77	118
+	+	67	35	145 85—75	1.25	—	14.1	0	0	3.65	91	2.80	100	77	117
+		80	33	195 100—90	1.09	83	14.2	0	0	3.55	79	2.38	[illegible]	67	102
		100	35	185 75—65	1.08	55	13.8	0	[illegible]	2.75	62	2.15	74	78	116
+		92	[illegible]	175 85—75	—	—	16.4	[illegible]	0	3.60	88	2.60	97	72	109
+		70	44	170 100—80	0.80	50	13.3	(+)	0	2.75	67	1.50	56	55	82
	+	85	42	180 90—80	1.19	76	14.4	0	0	3.15	76	2.65	93	84	122
+	+	67	24	125 65—55	1.04	109	13.1	0	0	[illegible]	112	—	—	—	—
+	+	75	46	150 90—85	1.06	93	14.2	0	0	4.38	90	3.60	103	82	114
+		81	41	190 80—65	0.97	51	12.0	(+)	0	2.33	103	1.78	104	76	101
		123	42	185 120—90	0.88	120	12.4	—	—	1.03	46	0.84	47	82	106
		63	41	175 85—80	0.89	37	14.5	0	0	2.50	84	1.83	80	73	91
		76	38	145 85—70	0.65	126	13.6	0	0	3.35	85	2.65	81	79	93
		53	53	180 105—100	1.17	64	12.0	0	0	3.50	89	2.60	105	74	114
		63	63	125 70—65	0.87	70	15.8	0	0	3.55	[illegible]	2.45	94	69	105
		57	57	190 105—100	1.15	72	12.0	0	+	3.60	89	2.50	89	69	100
		69	69	120 70—60	1.13	55	10.2	0	0	2.95	70	1.85	[illegible]	63	90
		8	85	145 95—85	0.69	163	14.1	0	0	3.00	67	2.20	69	73	101
		64	64	150 100—95	0.85	68	16.1	0	+	4.25	96	3.15	96	74	100
		68	68	140 90—85	0.96	—	13.9	0	0	4.53	93	3.10	82	68	87
		69	69	120 90—80	0.76	143	15.2	0	0	5.85	108	4.45	100	76	90

Table A

Patient no	Diagnosis	Age at examination in years	Sex	Height in cm	Body weight in kg	Previous history	Total heart volume in ml	Relative heart volume in ml/sq m BSA	Functional class	Age at first diagnosis of CHD in years	
Group B											
1	Unknown	81	♂	169	63	1961 cholecystit	1020	600	II	78	
[illegible]	Unknown	76	♂	158	63	Prost hyperpl	1100	700	III	72	
3	Unknown	76	♂	175	74	1943 empyema	1200	640	III	76	
4	Unknown	74	♂	172	78		1140	600	II	69	
5	Misc	73	♂	164	63	1956 cer concussion 1958 influenza	840	485	II	66	
[illegible]	Misc	73	♂	183	104	1917 lues 1959 pulm edema gall bladder dis	1820	860	III	68	
7	Unknown	71	♂	163	67		710	415	II	68	
8	Unknown	69	♂	170	64		840	480	III	69	
9	Unknown	69	♂	180	76	1913 arthralg	930	480	II	69	
10	Nonacute cor heart dis	68	♂	180	100		1380	630	III	67	1
11	Unknown	68	♂	172	80		1050	550	II	61	6
12	Misc	66	♂	171	73	Ulcer colit 1958 myocardit	890	480	II	61	7
13	Unknown	61	♂	169	73		940	510	II	45	20
14	Unknown	60	♂	167	64		940	540	III	55	6
15	Unknown	55	♂	181	83		1050	510	II	48	8
6	Unknown	75	♀	153	58	Arthralg	870	570	II	73	46
7	Rheum heart dis	57	♀	145	51	1943 icterus 1944 ac rheum fev 1950 op hyper parathyr 1951 op ureterolith	550	410	III	45	154
3	Misc	54	♀	159	73	1953 myocardit	890	510	II	48	84
[illegible]	Unknown	28	♀	171	61		610	350	II	27	15
p											
	Ac myocard inf	74	♂	171	62	1957 ac myocard inf	830	450	II	68	2d(92)
	Ac myocard inf	67	♂	169	70	1958 ac myocard inf	600	450	II	62	12d(77)
	Ac myocard inf	60	♂	167	72	1948 gastr ulc 1960 ac myocard inf	1050	600	III	–	2d(44)
	Rheum heart dis	59	♂	170	62	Polyarthrit Aort and mitr valv dis	1040	610	II	50	11d(114)
	Ac myocard inf	54	♂	173	75	1947 op gastr ulc	880	415	II	40	2d(67)
	Misc	49	♂	170	77	1958 ac gastr enterit and myocardit	700	390	I	44	1d([illegible])
	Misc	37	♂	176	72	Reiter	640	340	I	35	2d(29)
	Rheum heart dis	22	♂	180	70	1958 ac rheum fev	670	3[illegible]5	I	16	2d(73)

TABLE A shows some data on the patients in the catheterization study (chapters V, VI, VII and VIII). Group B consists of patients having complete heart block (CHB) at catheterization and group T of patients having had a transient CHB but sinus rhythm at catheterization. The functional classification was done according to the criteria of the New York Heart Association. The figures in brackets in group T of the column "Duration of CHB" mean the time in months between the beginning of CHB and the catheterization and the figures followed by "d" means the duration in days of CHB in these patients with transient CHB. No sign in the column "Bundle branch block type" indicates a normal QRS duration. Patient number 6 had atrial fibrillation at catheterization. The two diastolic blood pressure values in the column "Blood pressure" indicate the values when the Korotkoff sounds showed the highest intensity and when they disappeared respectively. For spirometric symbols see Abbreviations. "% pred." means the value obtained in % of the *normal values referred to in chapter II*.

Table A (continued)

Patient no	Diagnosis	Spirometric data in ATPS: FRC l	FRC % pred	TLC l	TLC % pred	MVV l/min	MVV % pred	I C I	Physical working capacity in kpm/min	Thera
Group B										
1	Unknown	4 24	107	6 52	102	78	75	10 6	100	
2	Unknown	3 82	116	5 72	103	38	40	12 3	200	Ephedrin
3	Unknown	4 32	112	6 40	97	69	64	12 0	300	Isuprel
4	Unknown	2 98	85	4 78	76	62	57	9 1	300	Digoxin
5	Misc	3 97	111	5 80	96	65	63	7 8	350	
6	Misc	2 10	61	3 75	56	40	34	10 5	600	
7	Unknown	4 60	129	6 80	112	79	75	13 0	300	Isuprel oc casion
8	Unknown	4 97	130	7 12	111	74	66	9 7	285	
9	Unknown	2 59	66	5 24	76	86	72	[illegible] 1	350	Isuprel
10	Nonacute cor heart dis	2 62	85	4 57	71	48	40	8 4	350	Ephedrine
11	Unknown	3 38	103	6 23	100	90	78	9 2	350	Ephedrine
12	Misc	3 82	109	4 92	78	62	53	9 7	400	
13	Unknown	2 89	87	4 49	72	116	94	9 7	600	
14	Unknown	3 85	109	6 90	111	—	—	9 1	300	Ephedrine
15	Unknown	2 45	71	5 48	80	131	92	9 4	600	
16	Unknown	1 86	101	3 49	100	42	53	10 2	75	Ephedrine
17	Rheum heart dis	0 88	58	1 43	47	26	27	—	50	Ephedrine
18	Misc	2 03	109	3 83	91	40	42	8 4	400	
19	Unknown	3 27	130	5 22	100	90	77	6 7	465	
Group T										
20	Ac myocard inf	4 10	103	5 97	92	94	88	11 5	675	
21	Ac myocard inf	3 53	98	6 23	99	106	93	8 2	675	
22	Ac myocard inf	3 72	112	6 02	98	92	66	12 1	675	
23	Rheum heart dis	3 30	88	4 95	76	64	50	10 2	300	Ephedrine oc casion
24	Ac myocard inf	2 57	85	4 32	68	76	63	9 7	350	
25	Misc	3 00	97	6 10	98	134	91	8 2	1 000	
26	Misc	4 03	121	7 18	109	156	96	5 5	900	
27	Rheum heart dis	3 26	94	6 66	95	148	79	8 0	900	

having had a transient CHB but sinus rhythm at catheterization RI and RII mean the resting values obtained 30 and 40 minutes after the catheters had been introduced O 1 O 3 and O 10 show values obtained after 1 3 and 10 minutes standing

Stroke volume in ml					Stroke index in ml					Blood pressure in mm Hg									
										Ascending aorta									
										Systolic					Diastolic				
RI	RII	O1	O3	O10	RI	RII	O1	O3	O10	RI	RII	O1	O3	O10	RI	RII	O1	O3	O10
137	138	111	100	90	76	91	64	53	52	206	207	222	200	194	83	75	91	83	81
93	100	7	80	76	[illegible]	67	43	49	47	183	180	170	159	163	64	64	64	61	63
199	135	120	178	91	107	73	64	68	48	186	179	176	156	172	58	69	66	64	67
133	128	95	90	83	0	67	50	47	44	193	203	217	189	176	67	70	73	66	64
13	141	126	102	102	79	81	72	59	59	[illegible]	311	345	303	285	96	107	124	189	95
109	118	100	98	93	50	54	46	45	43	153	148	157	143	148	75	69	73	71	77
135	127	119	100	78	81	74	0	53	46	200	190	203	186	163	64	64	71	66	71
111	105	82	74	74	63	60	47	42	42	141	149	129	133	123	62	71	68	67	70
110	130	114	121	120	56	67	58	64	42	223	238	246	235	270	65	86	103	103	113
144	144	142	124	103	66	66	65	57	47	205	199	276	209	195	52	53	71	61	62
120	117	86	[illegible]	89	62	61	45	46	46	[illegible]	163	168	152	168	76	75	83	76	81
113	111	116	93	88	61	60	63	51	48	254	260	259	262	259	95	85	103	86	83
[illegible]	87	56	54	45	45	47	30	29	24	201	203	187	187	173	85	89	82	75	69
107	100	131	87	81	62	58	76	51	47	191	19	181	171	156	69	70	65	65	66
112	124	105	85	68	54	60	51	41	33	140	137	153	150	124	77	73	70	87	86
99	95	75	73	63	64	62	49	47	41	190	204	200	204	183	62	67	70	76	66
82	80	65	68	60	60	58	4	50	44	188	175	221	173	179	92	74	129	90	97
98	9	85	[illegible]	4	56	55	48	47	42	210	200	197	180	160	81	78	83	78	75
147	143	100	108	07	85	[illegible]	58	63	56	[illegible]	169	166	154	144	79	79	93	91	88
119	118	100	93	83	68	65	55	51	46	195	19	201	191	181	7	77	83	82	77
26	*22*	*3*	*40*	*17*	*14*	*11*	*19*	*9*	*9*	*34*	*41*	*45*	*40*	*45*	*13*	*19*	*19*	*29*	*14*
19	19	19	19	19	19	19	19	19	19	19	19	19	19	[illegible]	19	19	19	19	19
96	89	56	31		55	51	37	18	—	191	194	181	111	—	97	87	94	71	—
60	63	53	59	46	34	35	30	33	26	139	138	139	139	142	77	75	74	64	8
87	83	65	[illegible]	6	46	49	36	29	32	173	197	181	171	159	93	105	105	95	107
67	5	56	56	4	39	43	32	32	27	164	[illegible]	159	143	142	83	79	76	71	78
80	8	60	57	44	40	39	30	29	21	163	139	154	147	111	95	[illegible]	99	95	98
97	89	0	67	53	49	47	37	33	28	186	186	176	165	137	100	[illegible]	104	104	80
91	[illegible]	65	1	68	49	51	35	38	36	124	121	115	128	119	86	83	89	90	85
81	85	80	6	54	43	45	43	36	29	115	105	131	128	102	87	79	105	102	7
[illegible]	83	63	57	53	44	45	3	31	28	138	157	15	[illegible]	134	89	87	9	[illegible]	87
12	*10*	*9*	*12*	*8*	*7*	*6*	*4*	*6*	*5*	*29*	*35*	*45*	*0*	*19*	*8*	*10*	*1*	*13*	*10*
8	8	8	8		8	8	8	8	–	8	8	[illegible]	8	7	8	[illegible]	8	8	7

TABLE B shows the individual hemodynamic data with means (M), standard deviations (SD) and number of observations (n) during the orthostatic test described in chapters V and VI. Group B consists of patients having complete heart block (CHB) at catheterization and group T of patients

Patient no	Atrial rate in beats/min					Ventricular rate in beats/min					Cardiac output in l/min					Cardiac index in l/min				
	RI	R II	O1	O3	O 10	RI	R II	O1	O3	O 10	RI	RII	O1	O3	O10	RI	RII	O1	O3	O1
Group B																				
1	84	77	[illegible]	79	78	37	36	38	39	39	4 9	5 7	4 2	3 9	3 5	2 8	3 3	2 4	2 3	2 0
2	100	100	97	97	97	44	43	43	45	45	4 1	4 3	3 3	3 6	3 4	2 5	2 7	2 0	2 2	2 1
3	76	63	60	63	67	26	32	30	32	32	5 0	4 4	3 6	4 1	2 9	2 7	2 3	1 9	2 2	1 5
4	86	79	79	81	84	40	40	42	40	41	5 3	5 1	4 0	3 6	3 4	2 8	2 7	2 1	1 9	1 8
5	100	100	118	—	100	41	41	43	44	42	5 6	5 8	5 4	4 5	4 3	3 2	3 3	3 1	2 6	2 5
6	—	—	—	—	—	43	40	43	41	43	4 7	4 7	4 3	4 0	4 0	2 2	2 2	2 0	1 8	1 9
7	76	64	80	78	79	32	30	32	32	32	4 4	3 8	3 8	3 2	2 5	2 6	2 2	2 2	1 9	1 5
8	63	67	67	70	69	35	38	39	39	39	3 9	4 0	3 2	2 9	2 9	2 2	2 3	1 8	1 7	1 7
9	129	100	99	108	125	30	27	29	29	30	3 3	3 5	3 3	3 6	3 6	1 7	1 8	1 7	1 8	1 8
10	86	80	79	68	70	34	32	33	34	34	4 9	4 6	4 7	4 2	3 5	2 2	2 1	2 2	1 9	1 6
11	87	75	87	87	73	35	35	37	38	36	4 2	4 1	3 2	3 4	3 2	2 3	2 1	1 7	1 8	1 7
12	65	65	69	65	65	38	38	37	41	43	1 3	4 2	4 3	3 8	3 8	2 3	2 3	2 3	2 1	2 1
13	69	69	69	69	70	46	46	54	57	55	3 8	4 0	3 0	3 1	2 5	2 1	2 2	1 6	1 7	1 4
14	51	51	62	70	70	30	31	32	31	32	3 2	3 1	4 2	2 7	2 6	1 9	1 8	2 4	1 6	1 5
15	60	61	60	65	62	41	38	39	40	40	4 6	4 7	4 1	3 4	2 7	2 3	2 3	2 0	1 7	1 3
16	74	75	75	75	73	40	40	40	41	41	3 9	3 8	3 0	3 0	2 6	2 5	2 5	1 9	1 9	1 7
17	97	105	111	113	115	39	40	43	47	47	3 2	3 2	2 8	3 2	2 8	2 3	2 3	2 0	2 3	2 0
18	57	54	67	67	63	40	39	41	42	43	3 9	3 8	3 5	3 5	3 2	2 2	2 2	2 0	2 0	1 8
19	71	74	80	91	86	36	37	37	37	38	5 3	5 3	3 7	4 0	3 7	3 1	3 1	2 2	2 3	2 2
M	[illegible]	76	80	79	80	37	37	39	39	40	4 3	4 3	3 8	3 6	3 2	2 4	2 [illegible]	2 1	2 0	1 8
SD	19	16	17	15	16	5	5	6	7	6	0 7	0 8	0 7	0 6	0 5	0 4	0 4	0 3	0 3	0 3
n	18	16	18	17	18	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19
Group T																				
20	53	56	59	51	—	53	56	59	54	—	5 1	4 9	3 3	1 7	—	2 9	2 8	1 9	1 0	—
21	63	60	62	70	69	63	60	62	70	69	3 8	3 8	3 3	4 1	3 2	2 1	2 1	1 8	2 3	1 8
22	57	55	57	57	60	57	55	57	57	60	4 7	4 9	3 7	3 0	3 4	2 6	2 7	2 1	1 7	1 9
23	69	65	68	70	68	69	65	68	70	68	4 6	4 9	3 8	3 9	3 2	2 6	2 8	2 2	2 2	1 8
24	85	81	85	86	94	85	81	85	86	94	6 8	6 3	5 1	4 9	4 1	3 4	3 2	2 6	2 5	2 1
25	64	61	63	69	62	64	61	63	69	62	5 9	5 4	4 4	4 3	3 3	3 1	2 9	2 3	2 3	1 8
26	68	67	80	75	76	68	67	80	75	76	6 2	6 4	5 2	5 3	5 2	3 3	3 4	2 8	2 8	2 9
27	69	66	74	87	94	69	66	74	87	94	5 6	5 6	5 9	5 8	5 1	3 0	3 0	3 1	3 1	2 [illegible]
M	66	64	69	71	75	66	64	69	71	75	5 3	5 3	4 3	[illegible] 1	3 9	2 9	2 9	2 [illegible]	2 [illegible]	2 1
SD	10	8	10	12	14	10	8	10	12	14	1 0	0 9	1 0	1 3	0 9	0 4	0 4	0 [illegible]	0 [illegible]	0 4
n	8	8	8	8	7	8	8	8	8	7	8	8	8	8	7	8	8	8	8	[illegible]

having had a transient CHB but sinus rhythm at catheterization RI and RII mean the resting values obtained 30 and 40 minutes after the catheters had been introduced O1 O3 and O10 show values obtained after 1 3 and 10 minutes standing

Stroke volume in ml					Stroke index in ml					Blood pressure in mm Hg									
										Ascending aorta									
										Systolic					Diastolic				
RI	RII	O1	O3	O10	RI	RII	O1	O3	O10	RI	RII	O1	O3	O10	RI	RII	O1	O3	O10
137	158	111	100	90	[illegible]	91	64	58	52	206	20	277	2 0	194	83	[illegible]	97	88	81
[illegible]	100	77	80	8	5	62	48	49	4	183	180	1 0	159	163	64	61	64	61	63
197	149	120	128	91	102	73	64	68	48	186	179	1 6	156	172	58	69	66	64	6
133	128	95	90	83	0	67	50	47	44	193	203	217	189	1 6	6	0	73	60	64
137	141	126	107	107	79	81	72	59	59	2 8	311	345	398	295	96	107	124	189	95
109	118	100	98	93	50	54	46	45	43	153	148	157	133	148		68	3	71	
138	12	119	100	8	81	4	0	58	46	200	190	203	186	163	64	64	1	66	1
111	10	82	4	4	63	60	47	42	42	141	149	129	133	123	69	71	68	67	0
110	130	114	124	120	56	67	58	61	62	223	238	246	235	2 0	65	86	103	103	113
144	144	147	124	103	66	66	65	57	4	205	193	276	200	195	57	54	71	61	[illegible]
1 0	117	86	89	89	62	61	45	46	46	1 9	163	168	152	168	6	73	83	6	81
113	111	116	93	88	61	60	63	51	48	254	260	2 9	262	2 9	95	85	103	86	83
8	87	[illegible]	54	45	45	47	30	29	24	204	203	187	187	1 3	9	[illegible]	82	5	[illegible]
107	100	131	87	81	62	58	6	51	47	191	197	181	1 1	156	69	0	65	65	66
112	124	105	85	68	54	60	51	41	33	140	13	153	150	123	7	3	0	8	[illegible]
[illegible]	95	5	3	63	61	67	49	47	41	190	201	200	201	183	62	6	0	6	66
87	80	65	[illegible]	60	60	58	4	50	44	188	1 5	291	1 3	1 9	92	4	129	90	9
99	97	85	83	74	56	55	48	47	42	210	200	197	180	160	[illegible]	8	83	8	5
14	143	100	108	97	[illegible]	83	58	63	56	1 4	169	166	164	144	9	9	93	91	88
118	116	100	93	83	66	6	5	51	58	19	19	201	191	181	7	75	83	8	77
8	*2*	*23*	*20*	*17*	*14*	*11*	*12*	*9*	*9*	*34*	*41*	*43*	*60*	*43*	*13*	*17*	*18*	*29*	*14*
19	19	19	19	19	19	19	19	19	19	[illegible]	19	19	19	19	19	19	19	19	19
96	89	56	31		55	51	32	18		194	194	181	111		97	87	97	71	—
60	63	53	59	46	34	35	30	43	26	139	138	139	139	142	7	5	4	84	8
87	89	65	53	[illegible]	46	49	36	29	32	1 3	19	181	1 1	159	93	105	105	95	102
67	5		56	47	39	43	32	32	2	164	1 8	158	149	142	83	9	6	1	8
80	8	60	57	41	40	39	30	29	21	168	139	154	147	144	95	81	98	95	98
97	89	0	67	53	49	47	3	33	28	196	186	1 6	16	137	100	93	104	104	[illegible]
91	96	65	1	68	49	51	35	38	36	124	121	115	128	119	86	83	[illegible]	90	85
81	85	8	6	54	43	45	43	36	29	115	105	131	128	107	87	9	105	107	
81	83	[illegible]	57	53	4		3	31	8	158	1	1	1	[illegible]	89	8	91	89	87
2	*10*	*9*	*1*	*4*		*6*	*4*	*6*	*5*	*9*	*35*	*25*	*40*	*19*	*6*	*10*	*1*	*13*	*10*
8	8	8	8		8	8	[illegible]	8		8	8	8	8		8	8	8	8	

Table B (continued)

Patient no	Blood pressure in mm Hg — Ascending aorta — Pulse pressure RI	RII	O1	O3	O10	Mean RI	RII	O1	O3	O10	Right atrial mean pressure in mm Hg RI	R II	O1	O3	O1
Group B															
1	123	132	130	112	113	119	112	130	122	109	8	7	6	9	—
2	119	116	106	98	100	92	125	96	92	93	11	9	6	5	4
3	128	110	110	92	105	93	100	100	—	91	9	8	5	—	5
4	126	133	144	123	112	109	106	111	106	98	9	9	3	2	1
5	182	204	221	209	190	164	158	201	163	145	13	10	11	—	4
[illegible]	78	80	84	62	71	91	99	90	96	100	12	15	13	10	9
7	136	126	132	120	92	100	93	108	—	95	8	7	8	—	6
8	79	78	61	66	53	83	95	85	90	83	6	6	4	4	3
9	158	152	143	132	157	178	124	137	—	164	15	13	14	—	13
10	153	146	155	148	133	91	100	109	96	97	9	11	9	8	6
11	103	88	85	76	87	102	105	—	—	103	9	8	—	—	3
12	159	175	156	176	176	134	133	132	137	129	15	12	13	6	10
13	109	114	105	112	105	128	123	118	102	98	9	9	4	3	2
14	122	127	116	106	90	100	103	—	—	85	8	9	—	—	—1
15	63	64	83	63	43	87	93	107	100	90	10	8	5	—	8
16	128	137	130	128	117	101	109	103	110	104	11	11	6	5	4
17	96	101	93	83	82	—	—	145	121	114	10	8	10	10	7
18	129	122	114	102	85	119	117	115	116	103	12	12	4	4	4
19	95	90	73	63	56	112	105	107	116	109	6	7	7	5	5
M	*120*	*121*	*118*	*109*	*104*	*111*	*111*	*117*	*112*	*106*	*10*	*9*	*8*	*6*	*5*
SD	*31*	*35*	*37*	*39*	*39*	*26*	*17*	*27*	*20*	*20*	*3*	*2*	*4*	*3*	*3*
n	19	19	19	19	19	18	18	17	14	19	19	19	17	12	18
Group T															
20	102	107	84	40	—	121	123	106	80	—	4	4	3	4	—
21	62	63	65	55	55	97	95	97	103	103	8	9	5	3	5
22	80	92	76	76	57	117	125	121	—	127	9	10	9	—	7
23	86	79	82	78	64	98	107	102	108	102	8	7	4	4	3
24	73	57	56	52	46	105	99	114	111	111	5	6	4	7	6
25	86	93	79	61	57	129	129	129	—	98	7	8	6	—	6
26	38	38	26	38	34	103	93	98	100	100	8	8	—1	—1	—2
27	33	26	26	26	25	92	89	121	110	87	6	6	—	2	—1
M	*70*	*69*	*62*	*53*	*48*	*108*	*108*	*111*	*102*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	*3*
SD	*24*	*25*	*24*	*18*	*14*	*13*	*16*	*12*	*12*	*12*	*2*	*2*	*3*	*3*	*4*
n	8	8	8	8	7	8	8	8	[illegible]	7	8	8	7	6	7

Systemic peripheral resistance in dyn sec cm ⁵					Central blood volume in ml					Mean transit time in secs				
RI	RII	O1	O3	O10	RI	RII	O1	O3	O10	RI	RII	O1	O3	O10
1810	14 2	2360	2316	—	2205	1993	1680	1625	1458	27	21	24	25	25
15 9	2156	2180	1931	2097	1640	1720	1210	1380	1360	21	24	22	23	[illegible]
1343	16 1	2109		23 0	2083	168	1 40	1913	1402	25	23	20	23	20
1 08	1520	2158	2309	2290	2650	2465	1933	1620	1643	30	29	29	27	23
2155	2039	2812	—	2621	2053	1933	1890	1650	15 7	22	20	21	[illegible]	22
1343	1428	1431	1718	1818	2998	2663	2657	2400	2400	37	34	3	36	36
16 1	1800	2103		2345	1 60	1647	1520	1387	1167	21	26	[illegible]	26	29
15 8	17 8	2023	23 0	2205	1690	1800	1547	1450	1407	26	27	29	30	20
3945	2535	29 9		3357	1 60	1867	1 05	1800	1 40	32	32	31	30	29
1337	1546	1 00	16 5	20 8	2287	2773	2507	2100	1975	28	29	32	30	33
1 0	1891	—	—	2498	1 50	1610	1333	1360	1333	25	21	25	21	2
2712	2302	2212	2755	2 03	1 97	1610	1619	1 83	1457	25	23	23	25	23
2503	2278	3037	2552	3089	1710	1867	1400	1447	1125	27	28	28	29	27
2299	2423	—		2644	1867	2118	2240	13 0	1213	35	41	32	30	29
1336	1445	1988	—	2127	1903	2037	1 77	14 3	1350	26	26	26	26	30
1844	2061	2394	2 9	30 4	1495	145	1250	1200	1127	23	23	25	24	26
	—	3853	27 2	3054	1067	1120	897	1013	933	20	21	19	19	20
2193	2208	2535	2558	2473	1495	1583	1233	1293	1297	23	25	22	22	23
1598	14 8	2160	2218	2246	1 67	16 8	1233	1400	1295	20	19	20	21	21
1890	*1891*	*2366*	*2331*	*2536*	*1893*	*[illegible] 8*	*16 1*	*1 9*	*1128*	*26*	*26*	*26*	*26*	*27*
830	*370*	*564*	*390*	*409*	*417*	*357*	*452*	*325*	*33*	*5*	*5*	*5*	*4*	*4*
18	18	17	12	18	19	19	19	19	19	19	19	19	19	19
1833	1911	2494	35 3		2040	2123	1595	1048		24	26	29	37	—
18 2	1809	2228	1949	2448	1583	1583	1375	1703	1387	25	25	25	25	26
183	18 6	2419		2821	1567	1633	1357	1250	1417	20	20	22	2	25
1564	1631	2061	2131	24 3	1840	1960	1520	1560	1280	21	21	24	21	24
11 5	*1180*	*1724*	*1696*	2047	1927	1890	1530	14 0	1293	17	[illegible]	18	[illegible]	19
1653	1 91	2234		2229	1573	1530	1320	1290	1155	16	17	[illegible]	18	21
1275	1086	1521	1523	1565	1860	1970	14 3	1502	14 3	[illegible]	18	17	17	17
127	116		1489	13 9	1960	2053	1 73	1740	1415	[illegible]	22	[illegible]	18	17
1 58	1567	2037	2060	2138	1795	1837	1468	1 [illegible]	13 1	21	21	21	23	21
299	*354*	*359*	*182*	*515*	*193*	*2?5*	*105*	*237*	*112*	*4*	*4*	*6*		*4*
8	8	7	8	7	8	8	8	8	7	8	8	8	8	7

Table B (continued)

Patient no	Blood pressure in mm Hg – Ascending aorta – Pulse pressure RI	RII	O1	O3	O10	Mean RI	RII	O1	O3	O10	Right atrial mean pressure in mm Hg RI	RII	O1	O3	O10
Group B															
1	123	132	130	112	113	119	112	130	122	109	8	7	6	9	—
2	119	116	106	98	100	92	125	96	92	93	11	9	6	5	4
3	128	110	110	92	105	93	100	100	—	91	9	[illegible]	5	—	5
4	126	133	144	123	112	109	106	111	106	98	9	9	3	2	1
5	182	201	221	209	190	164	158	201	163	145	13	10	11	—	4
6	78	80	84	62	71	91	99	90	96	100	12	15	13	10	9
7	136	126	132	120	92	100	93	108	—	95	8	7	8	—	[illegible]
8	79	78	61	66	53	83	95	85	90	83	6	6	4	4	3
9	158	152	143	132	157	178	124	137	—	164	15	13	14	—	13
10	153	146	155	148	133	91	100	109	96	97	9	11	9	8	6
11	103	[illegible]	85	76	87	102	105	—	—	103	9	8	—	—	3
12	159	175	156	176	176	134	133	132	137	129	15	12	13	6	10
13	109	114	105	112	105	128	123	118	102	98	9	9	4	3	2
14	122	127	116	106	90	100	103	—	—	85	8	9	—	—	—1
15	63	64	83	63	43	87	93	107	100	90	10	8	5	—	8
16	128	137	130	128	117	101	109	103	110	104	11	11	6	5	4
17	96	101	93	83	82	—	—	145	121	114	10	8	10	10	7
18	129	122	114	102	85	119	117	115	116	103	12	12	4	4	4
19	95	90	73	63	56	112	105	107	116	109	6	7	7	5	5
M	120	121	118	109	104	111	111	117	113	100	10	9	8	[illegible]	7
SD	*31*	*35*	*37*	*39*	*39*	*26*	*17*	*27*	*20*	*20*	*3*	*2*	*4*	*3*	*3*
n	*19*	*19*	*19*	*19*	*19*	*18*	*18*	17	14	19	19	19	17	12	18
Group T															
20	102	107	84	40	—	121	123	106	80	—	4	4	3	4	—
21	62	63	65	55	55	97	95	97	103	103	8	9	5	3	5
22	80	92	76	76	57	117	125	121	—	127	9	10	9	—	7
23	86	79	82	78	64	98	107	102	108	102	8	7	4	4	3
24	73	57	56	52	46	105	99	114	111	111	5	6	4	7	[illegible]
25	86	93	79	61	57	129	129	129	—	98	7	8	6	—	6
26	38	38	26	38	34	103	93	98	100	100	8	8	—1	—1	—2
27	33	26	26	26	25	92	89	121	110	87	6	6	—	2	—1
M	70	69	62	73	48	108	108	111	102	[illegible]	7	7	[illegible]	3	3
SD	*24*	*28*	[illegible]	*18*	*14*	*13*	*16*	*12*	*12*	*12*	*2*	*2*	*3*	*3*	*4*
n	8	8	8	8	7	8	8	[illegible]	6	7	8	8	7	[illegible]	7

exercise The figure after E and AE indicates time in minutes E 1 denotes values obtained after 1 minute s exercise and AE 10 values obtained 10 minutes after the end of exercise The alveolar arterial oxygen pressure difference PAO₂—PaO₂ in mm Hg and the quotient between dead space and tidal volume (V_D/V_T) were calculated as described by Bersen (12) [1] denotes cardiac output determined with the forward triangle method

Cardiac index in l min						Stroke volume in ml						Stroke index in ml					
R	E1	E4	E8	AE4	AE 10	R	E1	E4	E8	AE4	AE 10	R	E1	E4	E8	AE4	AE 10
24	39	40	60	27	23	108	117	117	151	118	103	62	68	69	87	68	60
25	27	30	28	22	19	84	100	100	90	80	69	52	62	62	56	49	43
21	[1]28	[1]34	[1]36	26	27	133	[1]161	[1]143	[1]153	136	111	71	[1]86	[1]76	[1]71	72	59
21	30	34	30	27	23	93	136	103	108	113	96	49	72	51	57	59	51
33	14	39	52	36	32	135	140	118	164	135	115	78	80	68	94	78	[illegible]
20	33	20	38	21	22	110	120	121	111	98	100	50	55	56	51	44	46
[illegible]0	24	28	33	19	22	106	121	133	139	94	93	[illegible]	71	78	81	[illegible]	54
23	30	31	35	22	19	114	133	149	163	106	92	65	76	85	93	61	53
19	23	28	—	23	22	123	141	157	—	152	145	66	72	81	—	78	74
18	20	—	—	20	19	126	143	—	—	143	128	59	66	—	—	66	59
19	19		—	24	21	112	95	—		139	114	58	49	—	—	72	59
20	34	30	40	26	22	90	77		85	104	82	49	42	—	46	57	45
19	30	36	41	24	22	55	86	80	85	90	81	42	47	43	46	49	46
20	[1]27	[1]22	21	23	—	110	[1]153	[1]123	120	134	—	61	[1]89	[1]72	70	78	—
18	31	33	33	28	23	97	160	160	156	143	118	47	78	78	76	69	57
23	25	27	—	23	25	88	87	100		83	95	57	46	63	—	57	62
27	31	36	37	21	23	73	83	78	64	44	60	53	65	57	47	32	44
24	28	38	44	20	17	108	64	69	82	73	65	61	36	39	47	41	37
29	34	40	46	33	38	139	100	117	130	154	183	81	59	68	76	90	106
22	29	33	30	25	23	106	117	117	119	113	102	59	65	46	67	82	57
04	*05*	*06*	*10*	*04*	*05*	*22*	*29*	*[illegible]5*	*33*	*30*	*30*	*1[illegible]*	*15*	*13*	*18*	*15*	*15*
18	19	17	15	19	18	19	19	16	15	19	18	19	19	16	15	19	18
22	[illegible]3	61	53	22	—	70	107	112	97	[illegible]9	—	40	61	61	56	33	—
18	38	39	43	24	22	53	75	63	70	57	55	30	42	35	39	32	31
25	43	49	[illegible]1	25	24	82	93	92	95	66	66	46	52	51	53	37	37
2	42	47	53	28	26	73	79	80	90	69	68	42	45	46	52	40	39
21	37	35	—	37	28	64	64	52	—	79	64	32	32	26	—	39	32
28	1	53	53	26	23	82	96	93	99	70	69	44	51	53	53	37	47
2[illegible]	[illegible]8	[illegible]2	66	24	26	81	120	101	109	6	56	43	64	54	59	30	30
[illegible]2	40	46	45	30	27	81	83	81	7	76	72	43	44	45	41	40	39
2	16	19	5[illegible]	27	2[illegible]	77	90	87	91	15	6	*8*	*9*	*7*	[illegible]	36	35
04	*10*	*10*	*08*	*05*	*0*	*11*	*18*	*[illegible]0*	*13*	*9*		*6*	*10*	*1[illegible]*	[illegible]	*4*	*4*
8	8	8	7	8	7	8	8	8	7	8	7	8	8	8	7	8	7

TABLE C shows the individual hemodynamic data with means (M), standard deviations (SD) and number of observations (n) *during the exercise test* described in chapters V and VII. Group B consists of patients having complete heart block (CHB) at catheterization and group T of patients having had a transient CHB but sinus rhythm at catheterization. R means resting values, E values obtained during exercise, AE values obtained after

Patient no	Work load in kpm/min	Exercise time in minutes	Atrial rate beats/min						Ventricular rate beats/min						Cardiac output in l/min					
			R	E1	E4	E8	AE4	AE10	R	E1	E4	E8	AE4	AE10	R	E1	E4	E8	AE4	AE10
Group B																				
1	150	8	83	120	111	120	100	92	38	58	60	68	39	39	4 1	6 8	7 0	10 3	4 6	4 0
[illegible]	200	8	97	—	—	—	120	109	44	43	48	50	45	45	3 7	4 3	4 8	4 5	3 6	3 1
3	300	8	71	100	—	—	109	91	30	33	44	51	36	45	4 0	5 3	6 3	6 8	4 9	5 0
4	300	8	69	69	93	120	73	69	42	42	62	64	46	45	3 9	5 7	8 4	6 9	5 2	4 3
5	300	8	100	107	154	158	115	111	43	43	57	55	46	48	5 8	6 0	6 7	9 0	6 2	5 5
6	200	8	—	—	—	—	—	—	40	60	53	70	47	48	4 4	7 2	6 4	7 8	4 5	4 8
7	200	8	84	92	140	145	102	104	33	34	36	41	35	40	3 5	4 1	4 8	5 7	3 3	3 7
8	200	8	60	95	93	93	71	70	35	40	37	38	36	36	4 0	5 3	5 5	6 2	3 8	3 3
9	200	4	100	135	150	—	109	112	29	32	35	—	29	29	3 7	4 5	5 5	—	4 4	4 2
10	300	1	79	—	—	—	100	94	31	30	—	—	30	32	3 9	4 3	—	—	4 3	4 1
11	200	3	82	100	—	—	105	98	33	39	—	—	33	35	3 7	3 7	—	—	4 6	4 0
12	200	8	66	130	—	175	72	75	40	62	—	86	45	49	3 6	6 3	5 5	7 3	4 7	4 0
13	300	8	70	106	122	132	89	83	60	65	82	88	50	49	3 5	5 6	6 6	7 5	4 5	4 1
14	100	8	57	100	98	98	72	63	31	30	31	30	29	31	3 4	4 6	3 8	3 6	3 9	—
15	300	8	54	—	—	92	75	67	39	40	43	43	40	40	3 8	6 4	6 9	6 7	5 7	4 7
16	100	4	75	—	—	—	81	78	40	45	41	—	40	40	3 5	3 9	4 1	—	3 5	3 8
17	50	8	107	120	120	160	—	135	41	47	63	80	66	53	3 0	4 2	4 9	5 1	2 9	3 2
18	200	[illegible]	65	120	160	143	94	91	40	78	98	94	48	46	4 3	5 0	6 7	7 7	3 5	3 0
19	200	8	71	110	135	133	95	90	36	58	58	61	37	36	5 0	5 8	6 8	7 9	5 7	6 6
M	211	[illegible]	77	107	125	131	93	91	37	47	53	61	41	41	3 9	5 2	5 8	6 0	4 4	4 [illegible]
SD	76	2	16	17	23	2[illegible]	16	19	10	16	18	20	9		0 6	1 0	1 0	1 7	0 9	0 9
n	19	19	18	14	11	12	17	18	19	19	16	15	19	19	19	19	17	15	19	18
Group T																				
20	300	8	54	86	95	95	67	62	51	86	95	95	67	62	3 8	9 2	10 6	9 2	3 9	—
21	300	8	62	91	109	110	75	71	62	91	109	110	75	71	3 3	6 8	6 9	7 7	4 3	3 9
22	300	8	55	[illegible]	97	97	68	67	55	83	97	97	68	67	4 5	7 7	8 9	9 2	4 5	4 4
23	200	8	60	92	103	103	71	65	60	92	103	103	71	68	4 4	7 3	8 2	9 3	4 9	4 6
24	300	4	75	115	132	—	93	88	75	115	132	—	93	88	4 8	7 4	6 9		7 3	5 6
25	300	8	65	92	101	100	69	62	65	92	101	100	69	62	5 3	8 8	10 0	9 9	1 8	4 3
26	300	8	67	107	115	115	81	86	67	107	115	115	81	81	[illegible] 1	12 8	11 6	12 4	[illegible]	4 9
27	300	8	75	92	102	104	74	71	75	92	102	104	74	71	6 1	7 6	8 6	8 0	5 4	5 1
M	288	8	[illegible]	95	107	103	75	72	[illegible]	95	107	103	7[illegible]	72	4 7	8 5	9 0	9 4	5 0	4 7
SD	35	1	8	11	12	[illegible]	9	10	8	11	1[illegible]		9	10	0 9	1 3	1 1	1 3	1 2	0 6
n	8	8	8	8	8	7	8	8	8	8	8	7	8	8	8	8	8	7	8	7

Blood pressure in mm Hg						Right atrial mean pressure in mm Hg						Systemic peripheral resistance in dyn sec cm⁻⁵					
Ascending aorta																	
Mean																	
R	L1	L4	L8	AL4	AL10	R	L1	L4	L8	AL4	AL10	R	L1	L4	L8	AL4	AL10
116	125	17[illegible]	127	117	90	6	9	12	16	7	2	2144	1363	1290	861	1911	1758
90	82	106	95	116	97	8	20	24	21	14	11	1[illegible]71	1152	13[illegible]5	1314	2264	2217
107	100	—	120	—	—	10	21	—	24	—	—	1838	1191	—	1129	—	—
121	137	109	100	102	107	5	19	20	20	10	4	23[illegible]7	1654	1111	1031	1414	1871
147	13[illegible]	147	131	131	137	9	12	15	15	6	3	1901	1665	1574	1030	1611	1947
89	117	174	137	101	107	10	21	23	23	11	9	1435	1066	1261	1168	1598	1832
117	110	—	122	—	95	8	16	—	16	—	6	237[illegible]	1832	—	1480	—	1922
93	95	104	107	93	88	5	10	13	12	6	6	1758	1282	1323	1160	1830	1096
179	90	—	—	123	121	14	26	—	—	18	13	2481	1137	—	—	1907	2055
109	105		—	105	100	10	23	—	—	15	11	2029	1431	—	—	1673	1735
98	93	—	—	102	98	9	16	—	—	11	6	1972	1663	—	—	1581	1838
67	1[illegible]6		184	124	124	6	20		1	9	8	1243	19[illegible]9	—	1825	1956	2318
118	143	162	162	121	118	8	19	19	17	9	6	2512	1770	1732	1545	1989	2183
94	—	—	—	89	89			—	—	—	4	2045	—	—	—	—	—
97	97	—	93	—	—	8	—	—	18		—	1872	—	—	[illegible]	—	—
107	104	102	—	10[illegible]	98	8	15	21	—	8	8	2261	1824	15[illegible]9	—	2147	1893
137	113	11[illegible]	140	—	113	9	15	18	16	—	6	3410	1865	1615	1630	—	2872
120	155	179	167	111	113	10	20	24	17	10	11	2044	2158	1849	1557	2306	2717
114	151	103	107	107	110	4	11	13	11	4	4	1[illegible]58	1929	1058	971	1444	1231
108	118	12[illegible]	127	110	106	8	16	18	17	10	7	2062	1[illegible]86	1432	1257	1831	1999
20	[illegible]6	26	[illegible]8	1[illegible]	14	[illegible]	5	5	4	4	3	466	839	[illegible]53	304	283	368
19	18	11	14	15	17	19	17	11	14	14	17	19	17	11	14	14	16
106	—	—	—		—	3	—	—	—	—	—	2166	—	—	—	—	—
106	104	11[illegible]	122	108	108	10	10	[illegible]	[illegible]	6	6	2325	1105	1205	1152	1896	2090
123	153	1[illegible]5	165	142	142	7	15	13	12	6	6	2060	1432	1455	1329	2415	2470
104	117	136	132	105	98	8	13	11	8	4	4	1744	1139	1218	1066	1647	1633
105	141	157	—	106	105	3	16	22	—	5	4	1698	1350	1564	—	1106	1441
120	117	13[illegible]	122	112	112	5	4	4	3	3	3	1[illegible]34	1026	1063	961	1815	2076
97	113	115	108	95	108	3		6	1	1	2	1391	662	[illegible]1	690	1664	1832
92	97	106	103	94	100	3	[illegible]	4	3	2	2	1166	957	948	999	1313	1536
107	120	13[illegible]	12[illegible]	103	110	5	10	10	6	[illegible]	3	1786	109[illegible]	1172	1033	169[illegible]	1861
19	20	25	[illegible]2	16	15	3	5		5	2	3	[illegible]98	[illegible]56	282	213	4[illegible]	362
8	7		6	7	7	8	7	–	6	7	7	8	7	7	6	7	7

Table C (continued)

Patient no	Work load in kpm/min	Exercise time in minutes	Blood pressure in mm Hg — Ascending aorta — Systolic: R	E1	L4	E8	AI 4	AI 10	Diastolic: R	E1	E4	L8	AL 4	AE 10	Pulse pressure: R	E1	E4	E8	AL 4	AE 10
Group B																				
1	150	8	209	216	231	235	219	174	81	88	88	83	79	61	128	128	143	152	140	113
2	200	8	170	161	187	207	219	190	60	52	58	66	74	61	110	109	129	141	145	129
3	300	8	197	180	254	245	200	186	77	64	108	120	71	72	120	116	146	125	129	114
4	300	8	213	232	238	257	191	172	76	89	62	67	67	69	137	143	176	190	127	103
5	300	8	279	270	260	291	257	245	93	83	93	107	78	83	186	187	167	184	179	162
6	200	8	143	183	200	239	167	170	65	90	90	102	72	77	78	93	110	137	95	93
7	200	8	227	203	220	227	166	193	85	70	73	78	64	75	142	133	147	149	102	118
8	200	8	148	168	183	173	158	159	66	70	69	[illegible]	70	69	82	98	114	105	88	90
9	200	4	221	190	193	—	223	231	83	66	67	—	80	87	138	124	126	—	143	144
10	300	1	226	231	—	—	240	226	65	61	—	—	61	61	161	170	—	—	179	165
11	200	3	169	183	—	—	203	187	71	70	—	—	67	72	98	113	—	—	136	115
12	200	8	217	259	—	274	247	243	62	114	—	116	95	93	155	145	—	158	152	150
13	300	8	207	221	246	261	219	210	82	98	108	103	81	79	125	123	138	158	138	131
14	100	8	178	184	178	176	175	172	76	67	64	65	64	64	102	117	114	111	111	105
15	300	8	137	157	163	163	127	133	73	77	73	77	60	67	64	80	90	86	67	66
16	100	4	204	204	210	—	193	193	69	62	64	—	58	58	135	142	146	—	135	135
17	50	8	220	213	213	213	160	156	93	100	103	83	80	95	127	113	110	130	80	61
18	200	8	207	241	261	252	178	165	82	113	126	116	76	81	125	128	135	136	102	[illegible]
19	200	8	179	258	197	190	166	176	83	98	75	67	72	83	96	160	122	123	91	93
M	211	7	197	208	213	227	195	189	76	81	83	88	72	74	122	127	132	139	124	111
SD	76	2	35	34	31	39	35	31	10	18	20	21	9	11	30	26	22	28	31	30
n	19	19	19	19	16	15	19	19	19	19	16	15	19	19	19	19	16	15	19	19
Group T																				
20	300	8	160	200	191	184	169	159	86	109	95	97	94	84	74	91	96	87	75	75
21	300	8	145	132	159	171	143	143	81	81	86	92	83	86	64	51	73	79	60	67
22	300	8	180	214	230	233	193	183	100	122	127	123	110	108	80	92	103	110	83	75
23	200	8	166	176	197	193	149	153	85	95	98	95	75	78	81	[illegible]	99	98	74	75
24	300	4	144	150	203	—	152	137	82	111	134	—	84	82	62	39	69	—	68	55
25	300	8	173	169	186	173	153	161	87	88	102	92	86	84	86	81	84	81	65	77
26	300	8	115	143	143	141	118	123	84	87	87	89	85	97	31	56	56	55	33	20
27	300	8	113	123	129	132	119	123	85	87	90	94	87	87	28	36	39	38	32	36
M	288	8	150	163	180	176	150	148	86	98	102	97	88	88	61	66	77	78	61	60
SD	35	1	25	32	34	33	25	21	6	15	18	12	10	10	22	23	22	25	19	40
n	8	8	8	8	8	7	8	8	8	8	8	7	8	8	8	8	[illegible]	7	8	8

Oxygen consumption in ml				Respiratory quotient				(a-v)O_2 difference in ml per 100 ml			
R	L8	AE4	AE10	R	L8	AE4	AE10	R	L8	AE4	AE10
196	[illegible]	2 0	209	0 82	1 06	1 02	0 85	4 8	7 6	5 9	5 2
209	480	29	241	0 5	1 05	0 94	0 6	5 6	10	8 ?	[illegible]
2 1	758	425	329	0 77	1 12	1 22	1 04	5 5	11 1	8 7	6 0
206	11 7	381	317	1 12	0 93	1 35	1 02	7 6	1 1	7 3	7 4
266	1049	415	306	1 00	0 95	1 06	0 91	4 6	11	6 7	5 6
316	1180	3 0	309	0 81	1 01	1 06	0 84	7 2	15 1	8 2	6 4
287	948	3 6	305	1 23	1 03	1 28	1 05	8 2	16 6	10 8	8 2
—	—	—	—						—	—	—
290		320	298	1 00		0 96	0 77	7 8	—	7 3	7 1
408	—	380	302	0 82		0 93	0 86	7 6	—	8 8	7 4
2 1		342	281	0 7		1 04	0 86	7 3	—	4	7 0
2 8	800	3 6	2 7	0 78	0 83	0 91	0 81	7 2	11 1	8 0	6 9
218	1?23	318	281	0 1	0 95	0 93	0 6	6 2	16 3	7 1	6 9
288	00	—	366	0 86	0 84	—	1 22	8 5	19 4	—	—
234	1004	319	260	0 83	0 92	1 07	0 88	6 2	15 0	5 6	5 5
—			—	—	—		—	—	—	—	—
187		204	1 8	0 3		0 86	0 83	6 1	—	7 0	5 6
186	—	2 2	344	0 73		1 05	0 81	4.3	—	7 8	11 5
279		21	227	0 85		0 86	1 03	4 6	—	3 8	3 4
250	9 0	3 9	284	0 86	0 97	1 03	0 90	6 5	13 8	7.4	6.8
43	234	65	49	0 15	0 09	0 14	0 13	1 4	3 6	1 6	1 7
17	11	16	17	17	11	16	17	17	11	16	16
271	1060	233	—	0 7	0 91	0 99	—	5 8	11 6	6 0	—
187	10 3	243	188	0 95	0 92	1 23	0 84	5	13 7	5 7	4 8
234	101	256	229	0 5	0 90	0 92	0 89	5 2	11 1	5 7	5 2
2 9	804	245	236	0 7	0 94	0 88	0 5	4	8 6	5 0	5 1
258			248	0 84		—	1 21	5 4	—	—	4 4
238	11 9	280	2 2	0 7	0 80	0 89	0 87	4 5	11 9	5 8	5 9
212	909	2	303	0 86	0 87	1 21	1 07	3 9	7 3	6 2	6 3
26	792	263	249	0 77	0 81	0 92	0 84	4 3	9 9	4 7	4 9
2 8	[illegible]	2 7	244	0 81	0 88	0 99	0 90	4.9	10 6	5 6	5 2
	145	18	34	0 0	0 06	0 13	0 14	0 7	2	0 5	0 7
8	7		7	8	7	7		8	7	7	

Table C (continued)

Patient no	Work load in kpm/min	Exercise time in minutes	Central blood volume in ml R	L1	L4	L8	AL4	AL10	Mean transit time in secs R	L1	L4	L8	AL 4	AL 10	Lactate concentration in mg per 100 ml R	L1	L4	L8	AL 4	AL 10
Group B																				
1	150	8	1708	2267	2450	3090	1687	1600	25	20	21	18	22	24	34	—	90	107	93	75
2	200	8	1480	1577	1680	1650	1380	1188	21	22	21	22	23	23	33	—	116	141	115	87
3	300	8	1800	—	—	—	1960	2083	27	—	—	—	24	25	31	—	116	176	190	132
4	300	8	1755	2915	3093	2990	1993	1863	27	31	29	26	23	26	27	—	77	104	86	65
5	300	8	1933	2700	2345	2250	1860	1742	20	27	21	15	18	19	30	—	132	134	114	95
6	200	8	2713	3600	2880	3250	2400	2480	37	30	27	25	32	31	44	—	83	102	95	80
7	200	8	1342	2050	2240	2185	1210	1233	23	30	28	23	22	20	46	—	120	140	100	83
8	200	8	1800	2208	2200	2170	1583	1375	27	25	21	21	25	25	26	—	38	38	33	25
9	200	4	1727	1950	2567	—	1907	1820	28	26	28	—	26	26	39	—	142	—	120	85
10	300	1	2080	2509	—	—	2222	2050	32	35	—	—	31	30	33	63	—	—	66	55
11	200	3	1542	1480	—	—	1763	1600	25	24	—	—	23	27	44	74	—	—	89	75
12	200	8	1380	2205	1650	1947	1567	1533	23	21	18	16	20	23	25	—	42	63	34	46
13	300	8	1633	2033	2420	2500	1800	1572	28	25	22	20	24	23	34	—	90	113	90	66
14	100	8	1700	—	—	2220	2015	—	30	—	—	37	31	—	34	—	51	50	34	30
15	300	8	1647	2987	3105	2792	1900	1723	26	28	27	25	20	22	41	—	60	64	41	41
16	100	4	1342	1755	1708	—	1633	1457	23	27	25	—	28	23	32	—	75	—	71	53
17	50	8	1000	1260	1552	1360	916	1013	20	18	19	16	19	19	39	—	61	67	57	45
18	200	8	1648	1917	2122	2182	1283	1250	23	23	19	17	22	25	35	—	150	142	116	35
19	200	8	1667	1933	2040	2238	1710	1980	20	20	18	17	18	18	22	—	62	60	47	37
M	211	7	1679	2211	2770	2345	1726	1653	26	27	23	21	24	24	34	69	79	100	85	67
SD	70	2	348	595	503	537	354	371	4	5	4	6	4	4	[illegible]	8	35	41	35	2
n	19	19	19	17	15	14	19	18	19	17	15	14	19	18	19	2	17	15	19	19
Group T																				
20	300	8	1710	2913	3357	2607	1495	—	27	19	19	17	23	—	22	—	47	47	34	29
21	300	8	1430	2153	2070	2182	1505	1430	26	19	18	17	21	22	29	—	62	59	49	39
22	300	8	1800	2310	2372	2300	1425	1393	24	18	16	15	19	19	47	—	81	81	63	59
23	200	8	1760	2555	2325	2480	1552	1610	24	21	17	16	19	21	27	—	60	60	43	37
24	300	4	1440	2097	1725	—	1947	1587	18	17	15	—	16	17	33	—	87		79	61
25	300	9	1678	2053	2500	2145	1440	1290	19	14	15	13	18	18	33	—	39	41	37	31
26	300	8	1710	2347	2513	2480	1275	1360	19	11	13	12	17	17	25	—	41	43	34	[illegible]
27	300	8	2033	2153	2580	2133	1867	1700	20	17	18	16	20	20	25	—	31	30	30	29
M	288	[illegible]	1697	2123	2530	2332	1563	1481	22	17	16	15	19	19	30	—	[illegible]	[illegible]	46	37
SD	35	1	1947	289	468	190	223	151	4	3	2	2	2	2	[illegible]	—	[illegible]	[illegible]	[illegible]	14
n	8	8	8	[illegible]	8	7	8	7	8	8	8	7	8	7	8		8	7	8	9

Oxygen consumption in ml				Respiratory quotient				(a–v)O_2 difference in ml per 100 ml			
R	E8	AE4	AE10	R	E8	AE4	AE10	R	E8	AE4	AE10
196	787	270	209	0 82	1 06	1 02	0 85	4 8	7 6	5 9	5 2
209	480	295	241	0 75	1 05	0 94	0 76	5 6	10 7	8 2	7 8
221	[illegible]	425	329	0 77	1 12	1 22	1 04	5 [illegible]	11 1	8 7	6 6
296	1177	381	317	1 12	0 93	1 35	1 02	7 6	17 1	7 3	7 4
276	1049	415	306	1 00	0 95	1 06	0 91	4 6	11 7	6 7	5 6
316	1180	370	309	0 81	1 01	1 06	0 84	7 2	15 1	8 2	6 4
287	948	356	305	1 23	1 03	1 28	1 05	8 2	16 6	10 8	8 2
—	—	—	—	—	—	—	—	—	—	—	—
290	—	320	298	1 00	—	0 96	0 77	7 8	—	7.3	7 1
298	—	380	302	0 82	—	0 93	0 86	7 6	—	8 8	7 4
271	—	342	281	0 77	—	1 04	0 86	7 3	—	7 4	7 0
258	809	376	277	0 78	0 83	0 91	0 81	7 2	11 1	8 0	6 9
218	1223	318	291	0 71	0 95	0 93	0 76	6 2	16 3	7 1	6 9
288	700	—	366	0 86	0 84	—	1 22	8 5	19 4	—	—
234	1003	319	260	0 83	0 92	1 07	0 88	6 2	15 0	5 6	5 5
—	—	—	—	—	—	—	—	—	—	—	—
182	—	201	178	0 73	—	0 86	0 83	6 1	—	7 0	5 6
186	—	272	344	0 73	—	1 05	0 81	4 3	—	7 8	11 5
273	—	217	227	0 85	—	0 86	1 03	4 6	—	3 8	3 4
250	890	329	284	0 88	0 97	1 03	0 90	6.	13 8	7 1	[illegible]
43	*234*	*65*	*49*	*0 15*	*0 09*	*0 14*	*0 13*	*1 4*	*3 6*	*1 6*	*1 7*
17	11	16	17	17	11	16	17	17	11	16	16
271	1060	233	—	0 77	0 91	0 99	—	5 8	11 6	6 0	—
187	1053	243	188	0 95	0 92	1 23	0 84	5 7	13 7	5 7	4 8
234	1017	256	229	0 75	0 90	0 92	0 89	5 2	11 1	5 7	5 2
209	804	245	236	0 77	0 94	0 88	0 75	4 7	8 6	5 0	5 1
258	—	—	218	0 84	—	—	1 11	5 4	—	—	4 4
238	1179	280	252	0 77	0 80	0 89	0 82	4.5	11 9	5 8	5 9
212	909	277	303	0 86	0 87	1 11	1 07	3 9	7 3	6 2	6 3
262	792	263	219	0 77	0 81	0 92	0 84	4 3	9 9	4 7	4 9
228	975	257	2	0 81	0 88	0 99	0 90	4.9	10 6	5 6	5.2
26	*115*	*13*	*34*	*0 07*	*0 06*	*0 15*	*0 14*	*0 7*	*2 2*	*0 5*	*0 7*
[illegible]	7	7	7	8	7	7	7	8	7	-	7

Table C (continued)

Patient no	Work load in kpm/min	Exercise time in minutes	Pa_{O_2} in mm Hg				Pa_{CO_2} in mm Hg				Arterial pH			
			R	L8	AL4	AL10	R	L8	AL4	AL10	R	L8	AL4	AL10
Group B														
1	150	[illegible]	76	74	—	73	34	32	—	32	7 45	7 41	—	7 43
2	200	8	75	89	—	75	34	26	—	33	7 44	—	—	—
3	300	8	72	74	—	78	40	33	—	33	7 44	7 31	—	7 33
4	300	8	95	90	—	89	30	30	—	21	7 46	7 41	—	7 56
5	300	8	92	84	—	94	27	26	—	19	7 49	7 36	—	7 47
6	200	8	79	74	—	83	38	36	—	36	7 44	7 37	—	7 40
7	200	8	104	92	—	105	24	23	—	16	7 49	7 40	—	7 55
8	200	[illegible]	87	76	—	90	43	39	—	42	7 37	7 38	—	7 39
9	200	4	90	—	—	80	25	—	—	28	7 48	—	—	—
10	300	1	84	—	—	85	39	—	—	38	7 36	—	—	7 39
11	200	3	80	—	—	83	33	—	—	32	7 41	—	—	7 40
12	200	8	74	63	—	67	32	34	—	33	7 43	—	—	—
13	300	8	80	60	—	80	39	34	—	37	7 39	7 37	—	7 38
14	100	8	95	96	—	102	16	19	—	15	7 59	7 51	—	7 59
15	300	8	87	81	—	85	35	34	—	34	7 39	7 40	—	7 40
16	100	4	85	—	—	92	43	—	—	42	7 42	—	—	—
17	50	8	58	50	—	65	40	47	—	42	7 40	7 38	—	7 39
18	200	8	82	73	—	74	42	38	—	39	7 42	7 32	—	7 37
19	200	8	102	—	95	109	35	—	34	32	7 41	—	7 35	7 40
M	211	7	84	77	95	85	33	32	34	32	[illegible]	7 39	7 35	[illegible]
SD	*76*	*2*	*11*	*13*	—	*12*	*8*	*7*	—	[illegible]	*0 05*	*0 05*	—	*0 03*
n	19	19	19	14	1	19	19	14	1	19	19	12	1	15
Group T														
20	300	8	91	81	70	89	31	35	34	34	7 49	7 39	7 42	7 43
21	300	8	87	88	—	85	35	36	—	34	7 46	7 41	—	7 44
22	300	8	70	80	—	82	12	39	—	38	7 45	7 42	—	7 46
23	200	8	80	78	—	76	37	38	—	39	—	7 36	—	—
24	300	4	89	—	84	—	32	—	30	—	7 40	—	—	—
25	300	8	78	84	—	91	39	38	—	37	7 38	—	—	—
26	*300*	*8*	*94*	*86*	—	*105*	*36*	*43*	—	*32*	*7 42*	*7 38*	—	*7 47*
27	300	8	85	86	—	89	40	39	—	38	7 40	7 39	—	7 39
M	208	8	84	83	82	88	37	38	32	36	[illegible]	7 39	7 42	[illegible]
SD	*35*	*1*	*3*	*4*	*4*	*9*	*4*	*3*	*3*	*3*	*0 01*	*0 02*	–	*0 03*
n	8	8	8	7	2	7	8	7	2	7	7	6	1	5

Standard bicarbonate in mEq l				$P_{AO_2}-P_{aO_2}$ in mm Hg				V_D/V_T			
R	E8	AL4	AL10	R	E8	AL4	AL10	R	E8	AL4	AL10
22	19	—	20	32	43	—	39	0.32	0.31	—	0.41
24	—	—	—	34	38	—	36	0.53	0.43	—	0.55
24.5	16		17	29	46	—	40	0.53	0.42	—	0.42
21	19	—	19	27	27	—	39	0.34	0.17	—	0.20
20	15	—	15	28	36	—	33	0.23	0.11	—	—
25	20	—	21	25	39	—	25	0.38	0.33	—	0.42
18.5	15	—	15.5	27	37	—	31	0.31	0.22	—	0.19
23.5	22		23.5	—	—	—	—	—	—	—	—
19	—	—		34	—	—	31	0.24	—	—	0.35
21	—		21.5	15	—	—	17	0.51	—	—	0.52
20	—	—	19.5	29	—	—	31	0.33	—	—	0.31
20.5	—		—	37	47	—	44	0.43	0.33	—	0.48
22.5	[illegible]	—	21	15	52	—	21	0.49	0.36	—	0.49
17	16	—	16	38	33	—	36	0.19	0.21	—	0.33
20.5	20	—	20	21	32	—	26	0.32	0.14	—	0.20
26	—	—	—	—	—	—	—		—	—	—
28	26	—	21	26	—	—	33	0.43	—	—	0.40
25.5	18.5	—	21.5	15		—	31	0.28	—	—	0.33
21	—	18	19	7	—	16	9	0.37	—	0.33	0.27
[illegible]	18.8	18.0	19.6	20	39	16	31	0.37	0.28	0.33	0.38
9	*3.2*	—	*2.7*	*9*	*7*	—	*9*	*0.11*	*0.11*	—	*0.10*
19	12	1	15	17	11	1	17	17	11	1	16
22.5	20.5	21	22	21	31	37	—	0.44	0.20	0.47	—
24	[illegible]	—	22	30	27	—	29	0.40	0.25	—	0.38
23.5	24	—	26	23	28	—	26	0.52	0.41	—	0.48
—	20.5	—	—	26	34	—	27	0.44	0.40	—	0.50
19	—	—	—	24	—	—	—	0.20	—	—	—
22	—	—	—	24	20	—	16	0.36	0.16	—	0.30
22	24	—	22.5	11	12	—	11	0.19	0.07	—	0.25
23.5	22.5	—	22	14	16	—	15	0.39	0.18	—	0.36
22.9	22.3	21.0	22.9	22	[illegible]	37	21	0.37	0.2	0.47	0.37
2.6	*1.6*	—	*1*	*7*	*8*	—	*8*	*0.12*	*0.13*	—	*0.11*
[illegible]	6	1	[illegible]	8	7	1	6	8	7	1	6

TABLE D shows the individual hemodynamic data with means (M), standard deviations (SD) and number of observations (n) during the atropine test described in chapters V and VIII

Group B consists of patients having complete heart block (CHB) at catheterization and group T of patients having had a transient CHB but sinus rhythm at catheterization R shows

Patient no	Atrial rate in beats/min			Ventricular rate in beats/min			Cardiac output in l/min			Cardiac index in l/min			Stroke volume in ml			Stroke index in ml			Blood pressure in mm Hg, Ascending aorta, Systolic		
	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10
Group B																					
1	91	98	100	40	51	54	4.6	4.5	5.8	2.7	2.6	3.4	115	88	107	66	51	62	184	209	184
2	107	115	115	45	46	46	3.3	3.2	3.6	2.0	2.0	2.2	73	70	78	45	43	48	167	157	118
3	86	101	98	32	32	32	3.0	3.4	3.5	1.6	1.8	1.9	94	106	109	50	56	58	147	147	163
4	70	90	81	41	45	43	4.6	4.3	4.1	2.4	2.3	2.2	112	96	95	59	51	50	200	178	163
5	105	109	105	44	44	43	5.2	6.6	4.9	3.0	3.8	2.8	118	150	114	69	86	66	276	247	223
6	—	—	—	54	60	56	3.8	4.7	4.8	1.7	2.2	2.2	70	78	86	32	36	39	141	157	135
7	88	115	109	33	37	36	3.3	2.8	2.8	1.9	1.6	1.6	100	76	78	58	44	46	159	166	163
8	70	93	92	37	38	37	4.0	3.6	3.6	2.3	2.1	2.1	109	95	97	62	54	55	142	148	139
9	100	112	112	29	29	30	3.9	3.8	3.4	2.0	1.9	1.7	134	131	113	69	67	58	193	191	186
10	86	102	115	32	35	35	4.6	4.3	4.2	2.1	2.0	1.9	144	123	120	66	56	55	208	222	199
11	88	105	95	38	43	40	3.4	3.6	3.1	1.8	1.9	1.6	69	84	78	46	44	40	168	181	159
12	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
13	79	95	91	48	55	53	4.1	2.7	3.9	2.2	1.5	2.1	85	49	74	49	27	40	187	187	181
14	56	58	64	31	32	31	[b]2.2	—	[b]4.6	[b]1.3	—	[b]2.7	[b]71	—	[b]148	[b]41	—	[b]86	181	181	181
15	60	65	60	40	40	40	4.2	—	5.1	2.0	—	2.5	105	—	128	51	—	[illegible]	147	154	121
16	77	87	86	40	43	43	3.4	3.2	3.2	2.2	2.1	2.1	85	74	71	55	48	48	210	200	200
17	125	140	140	49	62	68	2.6	2.2	2.0	1.9	1.6	1.5	53	35	29	39	26	21	153	161	144
18	86	105	100	45	78	68	3.0	3.5	3.0	1.7	2.0	1.7	67	45	44	38	26	25	155	153	142
19	79	120	120	57	10	57	4.9	5.7	5.1	2.8	3.3	3.0	86	143	89	50	83	52	200	166	193
M	87	104	100	44	45	45	3.8	3.9	3.9	2.1	2.2	2.2	93	90	92	52	50	51	179	176	167
SD	17	19	19	8	12	12	0.8	1.1	1.0	0.4	0.6	0.5	[illegible]	31	29	11	18	15	34	[illegible]	2
n	17	17	17	18	18	18	19	16	18	18	16	18	18	16	18	18	16	18	18	18	18
Group T																					
20	55	86	67	55	86	67	4.1	—	3.9	2.4	—	2.2	75	—	55	43	—	33	169	221	141
21	70	79	80	70	79	80	3.5	4.0	3.6	2.0	2.2	2.0	50	51	45	28	28	24	138	143	143
22	64	71	70	64	71	70	4.5	4.9	4.8	2.5	2.7	2.7	70	69	69	39	39	39	197	203	197
23	65	69	74	65	69	74	4.2	4.0	4.1	2.4	2.3	2.4	65	59	55	37	33	32	166	156	154
24	88	100	102	88	100	102	5.7	5.0	5.4	2.9	2.5	2.7	65	50	53	33	25	27	135	129	124
25	67	92	90	67	92	90	5.4	5.1	4.8	2.9	2.7	2.6	61	55	53	44	29	25	167	147	139
26	75	105	109	75	105	109	4.3	4.1	4.9	2.3	2.2	2.6	57	49	45	30	21	21	115	110	117
27	70	91	88	70	91	88	5.3	6.3	5.6	2.8	3.4	3.0	76	69	61	40	37	31	113	116	120
M	69	87	85	69	87	85	4.6	4.8	4.8	2.5	2.6	2.5	67	56	55	37	30	30	150	153	141
SD	10	13	13	10	13	15	0.8	0.6	0.7	0.3	0.4	0.3	10	11	5	6	6	5	30	40	[illegible]
n	8	8	8	8	8	8	8	7	8	8	7	8	8	7	8	8	7	8	8	8	8

values before A 2 and A 10 values obtained 2 and 10 minutes after the intravenous administration of 0 1 mg atropine sulfate/10 kg body weight Patient number 12 was omitted from this final part of the catheterization study because of back pains See further legend table C

Blood pressure in mm Hg																				
Ascending aorta									Right atrial mean pressure in mm Hg			Systemic peripheral resistance in dyn sec cm[-5]			Central blood volume in ml			Mean transit time in secs		
Diastole			Pulse pressure			Mean														
R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10
81	103	97	103	105	92	114	131	114	5	5	5	1894	2238	1502	1840	1575	2127	24	21	22
55	59	52	111	93	96	92	89	77	6	7	3	2033	2018	1643	1320	1227	1380	24	23	23
60	60	77	87	87	86	87	82	98	9	8	9	2078	1739	2032	1550	1757	1575	31	31	27
66	63	59	134	115	104	100	91	91	7	2	6	1616	1654	1657	1993	1863	1708	26	26	25
82	86	81	194	161	142	136	119	119	9	5	2	1952	1380	1908	1820	2420	1797	21	[illegible]	22
69	72	69	72	81	66	88	117	87	8	8	7	1683	1854	1332	2090	2272	2180	33	29	31
63	64	75	96	102	[illegible]	[illegible]	92	93	6	5	5	1986	2483	2512	1265	1120	1120	23	24	24
69	71	64	74	75	75	93	88	95	6	5	5	1738	1843	1998	1733	1560	1560	26	26	26
77	73	73	116	118	113	106	104	101	9	8	8	1983	2019	2186	1895	1710	1700	29	27	30
58	65	53	150	157	146	104	111	91	9	10	5	1650	1877	1636	2453	2078	1960	32	29	28
76	84	74	92	97	84	102	103	97	3	5	4	2327	2176	2397	1417	1390	1292	25	23	25
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
70	84	79	117	103	102	110	124	118	[illegible]	6	7	2027	3493	2275	1709	1035	1363	25	23	21
73	80	70	108	104	111	99	109	100	5	8	6	[1]3414	—	[1]1633	—	—	—	—	—	—
73	75	62	74	79	59	100	95	82	8	9	9	1751	—	1144	1610	—	1870	23	—	22
71	64	68	139	136	132	100	108	109	9	5	6	2139	2573	2549	1303	1250	1280	23	24	24
87	104	90	56	60	54	107	117	107	6	8	7	3105	3959	3096	867	733	800	20	20	18
77	90	90	78	62	52	90	106	106	8	7	6	2184	2261	2664	1250	1225	1100	25	21	22
85	88	78	115	78	105	118	113	119	4	3	3	1859	1542	1818	1633	1805	1615	20	19	19
72	77	73	107	101	9[illegible]	10[illegible]	106	100	7	6	6	2082	2196	20[illegible]9	163[illegible]	1765	1561	2[illegible]	21	2[illegible]
9	*11*	*12*	*33*	*29*	*34*	*12*	*14*	*13*	*2*	*2*	*2*	*473*	*684*	*651*	*3[illegible]9*	*4[illegible]3*	*439*	*4*	*4*	*4*
18	18	18	18	18	18	18	[illegible]	18	18	18	18	[illegible]	16	[illegible]	17	16	17	17	16	17
92	132	88	7	83	56	117	100	—	5	3	—	2183	—	—	1640	—	1430	24	—	22
81	83	86	5	60	57	98	102	105	6	5	5	2101	1938	2220	1342	1400	1320	23	21	23
107	[illegible]	103	91	109	84	144	119	139	7	5	5	2133	1859	2185	1425	1389	1440	19	17	19
85	81	81	81	75	73	102	100	102	[illegible]	5	3	1846	1898	1930	1470	1490	1503	21	21	22
81	78	78	54	50	46	97	98	92	3	3	2	1318	1519	1332	1710	1417	1530	28	17	17
87	97	88	80	50	51	112	113	107	6	2	2	1569	1739	1748	1620	1445	1280	18	17	16
88	87	93	27	23	24	111	93	105	3	1	1	2007	1793	1696	1362	1230	1358	19	18	17
80	83	90	33	33	30	91	93	105	3	2	−1	1327	1154	1513	1767	1785	1597	20	17	17
88	9[illegible]	88	63	61	53	103	110	108	5	3	2	18[illegible]8	1700	1803	15[illegible]2	1[illegible]38	1[illegible]33	20	18	18
9	*13*	*8*	*24*	*9*	*20*	*1[illegible]*	*29*	*15*	*2*	*2*	*2*	*410*	*275*	*331*	*[illegible]3*	*164*	*104*	*2*	*2*	*3*
8	8	8	8	8	8	8	8	7	8	8	7	8	7	7	8	7	8	8	7	8

TABLE D shows the individual hemodynamic data with means (M), standard deviations (SD) and number of observations (n) during the atropine test described in chapters V and VIII. Group B consists of patients having complete heart block (CHB) at catheterization and group T of patients having had a transient CHB but sinus rhythm at catheterization. R shows

Patient no	Atrial rate in beats/min			Ventricular rate in beats/min			Cardiac output in 1 min			Cardiac index in l/min			Stroke volume in ml			Stroke index in ml			Blood pressure in mm Hg, Ascending aorta, Systolic		
	R	A2	A10	R	A2	A 10	R	A2	A10	R	A2	A10	R	A2	A 10	R	A2	A 10	R	A2	A10
Group B																							
1	91	98	100	40	51	54	4 6	4 5	5 8	2 7	2 6	3 4	115	88	107	66	51	62	184	209	184
2	107	115	115	45	46	46	3 3	3 2	3 6	2 0	2 0	2 2	73	70	78	45	43	48	167	157	148
3	86	101	98	32	32	32	3 0	3 4	3 5	1 6	1 8	1 9	94	106	100	50	56	58	147	147	163
4	70	90	81	41	45	43	4 6	4 3	4 1	2 4	2 3	2 2	112	96	95	59	51	50	200	178	163
5	105	109	105	44	44	43	5 2	6 6	4 9	3 0	3 8	2 8	118	150	114	68	86	66	276	247	223
6	—	—	—	54	60	56	3 8	4 7	4 8	1 7	2 2	2 2	70	78	86	32	36	39	141	153	135
7	[illegible]	115	109	33	37	36	3 3	2 8	2 8	1 9	1 6	1 6	100	76	78	58	44	46	150	166	163
8	70	93	92	37	38	37	4 0	3 6	3 6	2 3	2 1	2 1	108	95	97	62	54	55	142	146	130
9	100	112	112	29	29	30	3 9	3 8	3 4	2 0	1 9	1 7	134	131	113	69	67	58	193	191	186
10	86	102	115	32	35	35	4 6	4 3	4 2	2 1	2 0	1 9	144	123	120	66	56	55	208	222	199
11	[illegible]	105	95	39	43	40	3 4	3 6	3 1	1 8	1 9	1 6	89	84	78	46	44	40	168	181	158
12	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
13	79	95	91	48	55	53	4 1	2 7	3 9	2 2	1 5	2 1	85	49	74	48	27	40	187	197	181
14	56	58	64	31	32	31	[1]2 2	—	[1]4 6	[1]1 3	—	[1]2 7	[1]71	—	[1]148	[1]41	—	[1]86	181	184	181
15	60	65	69	40	40	40	4 2	—	5 1	2 0	—	2 5	105	—	128	51	—	62	117	154	121
16	77	87	86	40	43	43	3 4	3 2	3 2	2 2	2 1	2 1	85	74	74	55	48	48	210	200	200
17	125	140	140	49	62	68	2 6	2 2	2 0	1 9	1 6	1 5	53	35	29	39	26	21	153	164	144
18	86	105	100	45	78	68	3 0	3 5	3 0	1 7	2 0	1 7	67	45	44	38	26	25	155	152	142
19	70	120	120	57	40	57	4 9	5 7	5 1	2 8	3 3	3 0	86	143	89	50	83	52	200	166	193
M	85	101	100	[illegible]	45	45	3 8	3 9	3 9	2 1	2 2	2 2	95	90	92	52	50	51	179	170	167
SD	17	19	19	6	12	12	0 8	1 1	1 0	0 4	0 6	0 5	24	34	23	11	13	15	34	[illegible]	2
n	17	17	17	18	18	18	18	16	18	18	16	18	18	16	18	18	16	18	18	18	15
Group T																							
20	55	86	67	55	86	67	4 1	—	3 9	2 4	—	2 2	75	—	58	43		33	169	221	144
21	70	79	80	70	79	80	3 5	4 0	3 6	2 0	2 2	2 0	50	51	45	28	28	24	138	143	143
22	64	71	70	64	71	70	4 5	4 9	4 8	2 5	2 7	2 7	70	69	69	39	35	38	197	203	187
23	65	69	74	65	69	74	4 2	4 0	4 1	2 4	2 3	2 4	65	58	55	34	33	32	[illegible]	156	154
24	88	100	102	88	100	102	5 7	5 0	5 4	2 9	2 5	2 7	65	58	57	33	25	27	115	128	124
25	67	92	90	67	92	90	5 4	5 1	4 8	2 9	2 7	2 6	81	55	53	44	29	28	167	117	139
26	75	105	109	75	105	109	4 3	4 1	4 9	2 3	2 2	2 6	57	39	45	30	21	24	115	110	117
27	70	91	88	70	91	88	5 3	6 3	5 6	2 8	3 4	3 0	76	69	64	40	37	34	111	116	120
M	69	87	85	69	87	85	[illegible]	[illegible]	[illegible]	[illegible]	2 6	[illegible]	67	51	55	37	30	30	170	173	[illegible]
SD	10	13	15	10	13	15	0 8	0 8	[illegible]	0 3	0 4	0 3	10	11	8	6	6	5	30	40	[illegible]
n	8	8	8	8	8	8	8	7	8	8	7	8	8	7	8	8	7	8	8	8	8

values before. A 2 and A 10 values obtained 2 and 10 minutes after the intravenous administration of 0.1 mg atropine sulfate/10 kg body weight. Patient number 12 was omitted from this final part of the catheterization study because of back pains. See further legend table C.

Blood pressure in mm Hg												Systemic peripheral resistance in dyn sec cm⁻⁵			Central blood volume in ml			Mean transit time in secs		
Ascending aorta									Right atrial mean pressure in mm Hg											
Diastolic			Pulse pressure			Mean														
R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10	R	A2	A10
81	103	92	103	106	92	114	131	114	5	5	5	1894	2238	1502	1840	1575	2127	24	21	22
56	59	52	111	98	90	92	89	77	6	7	3	2033	2045	1613	1320	1227	1380	24	23	[illegible]
60	60	77	87	87	88	87	82	98	9	8	9	2078	1739	2032	1550	1757	1575	31	31	27
66	63	53	134	115	104	100	91	91	7	2	6	1616	1654	1657	1993	1863	1708	26	26	25
82	86	81	194	161	142	136	119	119	9	5	2	1952	1380	1903	1820	2420	1797	21	22	[illegible]
69	72	69	72	81	66	88	117	87	8	8	7	1683	1854	1332	2090	2272	2180	23	29	31
[illegible]	64	75	96	102	88	[illegible]	92	93	6	5	5	1936	2483	2512	1265	1120	1120	23	24	[illegible]
63	71	61	74	75	75	93	88	95	6	5	5	1738	1843	1995	1733	1560	1560	26	28	[illegible]
77	73	73	116	118	113	106	104	101	9	8	8	1988	2019	2186	1885	1710	1700	29	27	[illegible]
58	65	53	150	157	146	104	111	91	9	10	5	1650	1877	1636	2153	2078	1960	32	29	[illegible]
76	81	74	92	97	84	102	103	97	3	5	4	2127	2176	2397	1417	1390	1292	25	24	25
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
[illegible]	84	73	117	103	102	110	124	118	[illegible]	6	7	2027	3493	2275	1705	1015	1365	25	23	21
73	80	70	108	104	111	99	109	100	5	8	6	[1]3414	—	[1]1633	—	—	—	—	—	—
73	75	62	74	79	59	100	95	82	8	9	9	1751	—	1144	1610	—	1870	23	—	22
71	64	68	130	136	132	100	108	105	9	5	6	2139	2573	2545	1303	1280	1280	23	24	24
87	104	90	66	60	54	107	117	10	6	8	7	3105	3959	3996	867	733	600	20	20	18
[illegible]	90	90	78	62	52	90	106	106	8	7	6	2184	2261	2664	1250	1225	1100	25	21	22
85	88	8	115	78	105	118	113	119	4	3	3	1859	1542	1818	1633	1605	1615	20	19	19
72	77	73	107	101	[illegible]	[illegible]	106	100	7	6	6	2082	2196	[illegible]	1632	1565	1561	25	24	[illegible]
9	14	10	33	29	25	13	14	13	[illegible]		2	[illegible]	[illegible]	651	379	463	435	4	4	4
18	18	18	19	18	18	18	[illegible]	19	18	18	18	18	16	18	17	16	17	17	16	17
92	132	88	7	89	56	117	160	—	5	3	—	2183	—	—	1640	—	1430	24	—	22
81	83	86	57	60	57	98	102	105	6	5	5	2101	1938	2220	1342	1400	1320	23	21	22
106	94	103	91	109	84	144	113	139	7	5	5	2433	1859	2185	1425	1333	1440	19	17	18
65	65	81	81	75	3	102	100	102	[illegible]	5	3	1846	1893	1930	1470	1400	1503	21	21	22
61	78	78	54	50	46	97	98	92	3	3	2	1318	1519	1332	1710	1417	1530	18	17	17
8	97	[illegible]	80	50	51	112	113	107	6	2	2	1569	1739	1748	1620	1445	1290	18	17	16
88	8	93	27	23	24	111	93	105	3	1	1	2007	1793	1696	1362	1230	1388	19	18	17
80	83	90	33	33	30	91	93	105	3	2	−1	1327	1154	1513	1767	1785	1587	20	17	17
88	92	86	[illegible]	61	53	109	110	108	5	3	2	[illegible]	1700	1803	[illegible]	[illegible]	1435	20	18	19
9	15	5	[illegible]	9	[illegible]	17	[illegible]	15	2	2		410	278	[illegible]	163	168	104	2	2	3
8	8	8	8	8	[illegible]	8	[illegible]	[illegible]	8	8	7	8	7	7	8	7	8	8	7	8

TABLE E shows the individual hemodynamic observations at rest, during (E) and after exercise (AE) in five patients with an artificial pacemaker, before (B) and one hour after (A) intravenous administration of digoxin (1

	Case	Atrial rate in beats/min	Ventricular rate in beats/min	CO in l/min	CI in l/min	SV in ml	SI in ml	Blood pressure in mm Hg: Ascending aorta: Systolic	Diastolic	Pulse pressure	Mean	Pulmonary artery: Systolic	Diastolic	Pulse pressure	Mean	[illegible]	[illegible]
B Rest I	1	67	71	3 8	2 1	54	30	181	81	100	110	39	18	21	26	16	8
	2	63	71	5 2	2 6	73	37	163	90	73	107	26	8	18	12	3	—1
	3	75	73	9 4	4 4	129	61	133	74	59	93	32	13	19	18	12	6
	4	73	73	3 4	2 1	47	29	159	90	69	110	29	16	13	21	21	11
	5	85	75	4 5	2 6	60	35	162	86	76	109	42	26	16	26	8	12
	M	73	73	5 [illegible]	2 8	73	38	160	83	75	106	3[illegible]	[illegible]	17	21	12	7
B Rest II	1	67	71	4 1	2 3	58	32	166	75	91	119	39	18	21	21	14	7
	2	67	71	5 1	2 6	72	36	180	100	80	110	27	7	20	13	2	—1
	3	68	73	8 7	4 1	119	56	135	78	57	92	32	10	22	17	12	3
	4	73	73	3 4	2 1	47	29	152	96	56	115	31	15	19	22	18	12
	5	83	75	4 3	2 5	57	33	168	95	73	112	43	19	24	28	10	11
	M	72	73	5 1	2 7	71	37	160	89	71	110	35	14	21	21	12	6
A Rest	1	71	71	4 1	2 4	62	34	155	74	81	112	30	13	17	20	9	5
	2	57	71	3 2	1 6	45	23	163	88	75	112	22	6	16	6	—1	—3
	3	64	73	7 6	3 6	104	49	127	78	49	98	23	10	13	13	8	5
	4	75	74	3 1	1 9	42	30	147	83	64	102	30	14	16	20	20	11
	5	89	75	4 1	2 4	55	32	147	81	66	110	30	22	8	21	—	5
	M	71	73	[illegible]5	2 [illegible]	61	3[illegible]	148	81	67	107	27	13	14	16	9	5
B 1 min E	1	125	73	5 3	2 9	73	40	194	86	108	113	47	24	23	27	18	16
	2	85	71	5 2	2 6	73	37	173	87	86	108	43	16	27	26	16	—
	3	94	73	6 7	3 2	92	43	163	85	78	99	39	10	29	19	19	9
	4	97	84	6 2	3 8	74	46	162	95	67	105	42	24	18	30	29	17
	5	103	75	4 8	2 8	64	37	182	98	84	130	62	33	29	42	16	23
	M	101	75	5 6	3 1	75	41	175	90	85	111	[illegible]7	21	25	29	20	18
A 1 min E	1	85	110	—	—	—	—	209	106	103	128	62	33	29	42	32	10
	2	71	71	6 2	3 1	87	44	187	90	97	120	47	15	32	26	9	4
	3	85	73	9 0	4 2	123	58	148	77	71	103	40	17	23	23	13	7
	4	81	80	6 7	4 1	84	52	163	90	73	103	43	21	22	24	22	12
	5	97	75	5 0	2 9	67	39	158	70	88	102	53	29	24	36	—	16
	M	84	82	6 7	3 6	90	48	173	87	86	111	49	23	26	30	19	10
B 4 min E	1	107	79	5 1	2 8	65	36	231	78	153	125	80	31	49	51	41	15
	2	103	71	5 4	2 7	76	38	—	—	—	—	55	17	38	32	21	—
	3	97	73	8 4	4 0	115	54	159	63	76	107	48	18	30	28	20	5
	4	92	92	6 4	4 0	70	43	170	88	82	113	51	23	28	35	31	17
	5	130	75	5 3	3 1	71	41	201	97	104	138	70	36	32	53	25	24
	M	106	78	6 1	3 3	79	42	190	87	10[illegible]	121	61	[illegible]5	35	40	28	15
A 4 min E	1	85	75	5 5	3 [illegible]	73	40	23[illegible]	102	133	137	69	31	38	41	31	13
	2	80	71	6 1	3 1	56	43	190	8[illegible]	10[illegible]	114	30	9	21	17	18	—
	3	86	73	9 2	4 3	126	59	148	71	77	100	45	18	27	21	16	8
	4	84	80	6 2	3 9	78	48	163	87	76	105	41	17	24	25	23	12
	5	115	75	5 0	2 9	67	39	252	147	105	172	68	36	32	42	—	20
	M	90	75	[illegible]	[illegible]	86	[illegible]	198	97	99	126	51	2[illegible]	28	30	[illegible]	17

mg/70 kg body weight) 1 min E denotes values at 1 minute's exercise 4 min AE denotes values at 4 minutes after exercise M indicates the mean values

Syst periph res in dyn sec cm^{-5}	TVR in dyn sec cm^{-5}	CBV in ml	MTT in secs	Left ventricular minute work per sq m BSA	Left ventricular stroke work index per sq m BSA	Right ventricular minute work per sq m BSA	Right ventricular stroke work index per sq m BSA	pH	PO_2 in mm Hg	PCO_2 in mm Hg	Stand bicarb in ml q?	Lactate in mg per 100 ml
2145	210	1267	20	2 68	39 35	0 51	7 34	7 43	75	38	24	32
1660	138	1733	20	3 63	52 33	0 46	6 54	7 30	73	43	20	48
740	51	3447	[illegible]	4 85	67 20	0 72	9 96	7 38	74	40	22	18
2327	[illegible]	1077	19	2.54	35 10	0 29	3 94	7 53	84	28	23	18
1723	320	1275	17	3 57	48 08	0 50	6 66	7 47	77	34	24	26
1719	1	1760	20	3 6	8 21	0.50	6.89	7 42	77	37	23	28
2183	195	1435	21	3 28	45 70	0 53	7 40	—	—	—	—	—
1739	172	1700	20	3 82	52 83	0 50	6 85	7 29	72	41	19	47
818	46	2165	17	4 46	60 93	0 78	10 66	7 40	73	42	21 5	—
2421	94	1020	18	2 77	38 26	0 29	3 91	7 54	87	27 5	23 5	—
1577	335	1218	17	3 47	45 78	0 55	7 63	7 43	70	41	26	—
1808	169	1568	19	3 50	48 71	0.54	7.30	7 42	76	38	23	47
1044	200	1467	20	3 36	47 63	0 49	6 94	7 43	78	37	23 5	36
2372	175	1227	23	2 46	35 35	0 20	2 82	7 37	74	37	21	37
978	[illegible]	2027	16	4 41	59 98	0 39	5.33	7 41	85	39	23 5	21
2316	0	1033	20	2 12	33 46	0 23	3 67	7 4[illegible]	84	29	20	24
2047	—	1093	18	—	—	0 52	6 96	7 43	75	35	22	27
2077	107	1369	19	3 09	[illegible] 11	0.37	5 1	7 [illegible]2	79	35	22	29
1463	136	1943	22	3 75	51 69	0 43	5 94	—	—	—	—	—
—	154	1820	21	3 25	46 29	—	—	—	—	—	—	—
1074	0	2010	18	3 48	46 78	0 44	5 85	—	—	—	—	—
1134	13	1550	15	3 93	47 55	0 67	8 13	—	—	—	—	—
1 82	433	1370	17	4 34	57 36	0 72	9 56	—	—	—	—	—
1363	1 7	1737	19	3 75	49 91	0.57	7 38	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—
1495	219	2170	21	4 68	66 42	0 93	13 16	—	—	—	—	—
852	89	2400	16	5 14	70 99	0 91	12 62	—	—	—	—	—
1085	24	1675	15	4 52	57 28	0 67	8 49	—	—	—	—	—
1375	—	1500	18	—	—	0 79	10 61	—	—	—	—	—
1202	111	1936	[illegible]	[illegible] 78	6 90	0 83	11 22	—	—	—	—	—
1724	157	1700	20	3 20	41 13	1 37	17 63	—	—	—	—	—
—	163	1710	19	—	—	—	—	—	—	—	—	71
970	76	2210	16	4 73	63 89	1 25	16 89	—	—	—	—	—
1190	50	1493	14	1 46	47 95	0 98	10 53	—	—	—	—	—
1719	422	1413	16	4 76	63 01	1 22	16 17	—	—	—	—	—
1403	174	1711	17	[illegible] 29	54 00	1 21	17 31	—	—	—	—	71
1802	160	1650	18	4 20	56 03	1 26	16 86	—	—	—	—	—
—	—	2135	21	4 05	56 14	—	—	—	—	—	—	52
799	69	2453	16	4 91	67 40	0 91	12 84	—	—	—	—	—
1109	26	1653	[illegible]	4 24	53 53	0 67	8 49	—	—	—	—	—
2130	—	1500	18	—	—	0 87	11 67	—	—	—	—	—
1 8	85	1878	[illegible]	4.37	58 28	0 91	12.17	—	—	—	—	52

TABLE E shows the individual hemodynamic observations at rest, during (E) and after exercise (AE) in five patients with an artificial pacemaker, before (B) and one hour after (A) intravenous administration of digoxin (1

	Case	Atrial rate in beats/min	Ventricular rate in beats/min	CO in l/min	CI in l/min	SV in ml	SI in ml	Blood pressure in mm Hg: Ascending aorta: Systolic	Diastolic	Pulse pressure	Mean	Pulmonary artery: Systolic	Diastolic	Pulse pressure	Mean	[illegible]	[illegible]
B Rest I	1	67	71	3 5	2 1	54	30	181	81	100	110	39	18	21	26	16	8
	[illegible]	63	71	5 2	2 6	73	37	163	90	73	107	26	8	18	12	3	—1
	3	75	73	9 4	4 4	129	61	133	74	59	93	32	13	19	18	12	6
	4	73	73	3 4	2 1	47	29	159	90	69	110	29	16	13	21	21	11
	5	85	75	4 5	2 6	60	35	162	86	76	109	42	26	16	26	8	12
	M	73	73	5 3	2 8	73	38	160	81	75	106	31	16	17	[illegible]	12	7
B Rest II	1	67	71	4 1	2 3	58	32	166	75	91	119	39	18	21	24	14	7
	2	67	71	5 1	2 6	72	36	180	100	80	110	27	7	20	13	2	—1
	3	68	73	8 7	4 1	119	56	135	78	57	92	32	10	22	17	12	3
	4	73	73	3 4	2 1	47	29	152	96	56	115	34	15	19	22	18	12
	[illegible]	83	75	4 3	2 5	57	33	168	95	73	112	43	19	24	28	10	11
	M	72	73	5 1	2 7	71	37	160	89	71	110	37	14	21	21	12	6
A Rest	1	71	71	4 4	2 4	62	34	155	74	81	112	30	13	17	20	9	5
	2	57	71	3 2	1 6	45	23	163	88	75	112	22	6	16	6	—1	—3
	3	64	73	7 6	3 6	104	49	127	78	49	98	23	10	13	13	8	5
	4	75	74	3 1	1 9	42	30	147	83	64	102	30	14	16	20	20	11
	5	88	75	4 1	2 4	55	32	147	91	66	110	30	22	8	21	—	5
	M	71	73	[illegible]	[illegible]	63	[illegible]	[illegible]	81	67	107	27	13	11	16	9	[illegible]
B 1 min E	1	125	73	5 3	2 9	73	40	194	86	108	113	47	24	23	27	18	16
	2	85	71	5 2	2 6	73	37	173	87	86	108	43	16	27	26	16	—
	3	94	73	6 7	3 2	92	43	163	85	78	99	39	10	29	19	19	9
	4	97	84	6 2	3 8	74	46	162	95	67	105	42	24	18	30	29	17
	5	103	75	4 8	2 8	64	37	182	98	84	130	62	33	29	42	16	23
	M	101	75	5 6	3 1	75	41	175	90	85	111	47	21	25	29	20	[illegible]
A 1 min E	1	85	110	—	—	—	—	209	106	103	128	62	33	29	42	32	10
	2	71	71	6 2	3 1	87	44	187	90	97	120	47	15	32	26	9	4
	3	85	73	9 0	4 2	123	58	148	77	71	103	40	17	23	23	13	7
	4	81	80	6 7	4 1	84	52	163	90	73	103	43	21	22	24	22	12
	5	97	75	5 0	2 9	67	39	158	70	89	102	53	29	24	36	—	16
	M	[illegible]	82	6 7	3 6	90	[illegible]	173	87	86	111	49	23	26	30	19	[illegible]
B 4 min E	1	107	79	5 1	2 8	65	36	231	78	153	125	60	31	49	51	41	15
	2	103	71	5 4	2 7	76	38	—	—	—	—	55	17	38	3[illegible]	21	—
	3	97	73	8 4	4 0	115	54	159	83	76	107	48	18	30	28	20	[illegible]
	4	92	92	6 4	4 0	70	43	170	88	62	113	51	23	28	35	31	17
	5	130	75	5 3	3 1	71	41	201	97	104	138	70	38	32	53	[illegible]	24
	M	106	78	6 1	3 3	79	42	190	87	103	[illegible]	[illegible]	25	35	[illegible]	28	15
A 4 min E	1	85	75	5 5	3 0	73	40	235	102	133	137	[illegible]	31	38	44	34	13
	2	80	71	6 1	3 1	86	43	190	85	105	114	30	9	21	17	18	—
	3	86	73	9 2	4 3	126	[illegible]	148	71	77	100	45	18	27	21	16	8
	4	84	80	6 2	3 8	78	45	163	87	76	105	41	17	21	[illegible]	23	12
	5	115	75	5 0	2 9	67	39	[illegible]	147	105	172	68	36	32	42	—	[illegible]
	M	90	75	6 1	[illegible]	86	[illegible]	198	98	99	126	51	22	28	30	23	17

S st [er] ... rea l ... ly v e r	I VR I ... n sec ... n	CBS ...	M[T] in s c s	Left ve tricular ...nute ork per sq ... BSA	Left ventricular troke wo k [in] ... per sq m BSA	Righ t ventricular ... ute worl per sq ... BSA	Right ventricular stroke ork in ... per s[q] m BSA	pH	PO₂ ... m Hg	PCO₂ ... m Hg	Sta ... bicarb ...	Lact te in ... per 100 ml
—	196	1[illegible]5[illegible]	19	3 30	41 6[illegible]	—	—	7 39	63	36	21	6[illegible]
1340	111	2058	19	4 17	58 18	1 12	15 64	7 34	[illegible]	38	19 5	71
64	61	25 8	17	4 62	63 39	0 83	12 04	7 40	[illegible]4	37	22	30
1[illegible]17		1625	[illegible]	4 57	52 55	—	—	7 49	90	29	21	36
1544	—	1570	16	—	—	1 39	18 55	7 38	69	37	21	94
12[illegible]	123	1867	17	4 17	[illegible]3 9	1 13	15 41	7 [illegible]0	72	3	21	9
1608	100	17 3	19	4 2[illegible]	59 84	1 10	15 56	42	63	36	2[illegible] 5	5[illegible]
1 46	148	1870	18	3 86	54 26	0 84	11 89	7 36	[illegible]	37	20	50
688	103	2693	16	5 48	4 26	1 04	14 14	7 42	85	37	23	24
1474	58	13 5	13	4 [illegible]1	53 22	0 51	6 43	7 47	60	32	23	31
1873	—	1 07	16		—	1 06	13 99	7 43	68	35	2[illegible]	49
1 6	10[illegible]	187	17	4	60 10	0 91	1[illegible] 10	7 [illegible]	73	35	22	51
1933	167	1433	20	3 10	38 6	0 59	34	—	—	—	—	[illegible]
2 40	171	1027	22	1 73	24 5	0 21	2 99	—	—	—	—	[illegible]
866	8	2040	17	3 47	47 94	0 46	6 39	—	—	—		[illegible]
2131	44	1080	18	2 66	37 52	0 27	3 9		—	—	—	30
1615		1200	15			0 6	10 06	—	—	—		69
18 7	11	13 6	18	2 7	3[illegible] 2	0 46	6 11		—		—	7
23 3	231	1[illegible]00	16	3 82	55 07	0 59	9 04					46
—	1 8	900	2[illegible]	2 08	28 1	—		—	—	—	—	41
9[illegible]	10	1600	18	2 67	37 13	0 42	5 83	—	—			20
2451	27	1000	20	2 20	30 06	0 [illegible]1	2 83	—	—	—	—	28
1815		1120	14			0 65	8 55	—	—		—	—
1078	126	1182	18	2.69	38 36	0 7	6 6		—	—	—	7
1634	105	1425	19	2 96	40 23	0 54	40	7 42	0	34	21	43
2320	155	1189	23	1 89	26 03	0 20	2 69	7 37	73	39	21	53
870	73	2182	17	3 2	51 68	0 49	6 80	7 41	8[illegible]	33	23	20
2[illegible]09	—	1070	18	2 57	35 50	0 03	0 39	7 53	81	[illegible]6	2[illegible]	25
1893	—	1077	17	—	—	0 45	6 12	7 39	[illegible]	37	21 5	53
1[illegible]7	141	1378	[illegible]	2 79	36.36	0 34	[illegible] 68	[illegible]	[illegible]7	35	2[illegible]	39
1850	196	1388	17	4 08	57 36	0 55	5	7 40	80	33	2[illegible] 5	39
		1137	22	—	—	—		7 39	[illegible]	33	19 5	3
03	69	3480	18	5 39	73 44	0 82	11 [illegible]2	43	86	33	24	18
24 5	23	1015	[illegible]1	1 98	24 [illegible]4	0 20	2 39	7 49	[illegible]	28	21	27
18 [illegible]		1100	15	—	—	0 50	6 47	7 46	9	35	21	33
166.	98	16[illegible]4	[illegible]	3 8	51 68	0 2	6 96	7 43	80	3	2[illegible]	31

Table E (continued)

	Case	Atrial rate in beats/min	Ventricular rate in beats/min	CO in l/min	CI in l/min	SV in ml	SI in ml	Blood pressure in mm Hg									
								Ascending aorta				Pulmonary artery					
								Systolic	Diastolic	Pulse pressure	Mean	Systolic	Diastolic	Pulse pressure	Mean	[illegible]	[illegible]
B 8 min F	1	120	79	4.9	2.7	62	34	225	73	152	129	79	36	43	51	39	—
	[illegible]	102	71	6.5	3.3	92	46	194	77	117	113	61	19	42	29	20	4
	3	96	73	9.1	4.3	125	59	144	74	70	95	43	18	25	23	16	8
	4	97	89	6.5	4.0	74	46	179	97	82	116	—	—	—	—	32	17
	5	136	75	5.7	3.3	76	44	207	93	114	134	73	38	35	52	—	21
	M	110	77	6.5	3.5	86	46	190	83	107	117	64	28	36	39	27	13
A 8 min E	1	120	70	5.6	3.1	80	44	225	76	149	132	67	34	33	39	32	13
	2	81	71	5.4	2.7	76	38	207	90	117	121	58	19	39	20	16	3
	3	88	73	10.1	4.8	138	65	140	64	76	95	43	18	25	24	11	8
	4	65	80	5.5	3.4	69	43	167	87	80	110	42	19	23	23	19	12
	5	122	75	6.4	3.7	85	49	245	145	100	166	69	39	30	41	—	20
	M	99	74	6.6	3.5	90	48	197	92	104	125	[illegible]	20	30	31	20	11
B 4 min AE	1	80	79	4.3	2.4	54	30	194	86	108	111	49	22	27	25	16	7
	2	75	71	2.8	1.4	39	20	173	93	80	93	14	5	9	8	2	—3
	3	69	73	7.2	3.4	90	47	114	68	46	82	29	8	21	14	7	4
	4	72	72	3.6	2.2	50	31	168	97	71	106	33	15	18	19	17	10
	5	100	75	4.8	2.8	61	37	175	84	91	109	54	26	28	32	—	12
	M	79	[illegible]	4.3	2.4	61	31	165	86	79	100	[illegible]	13	21	20	11	6
A 4 min AE	1	88	70	4.5	2.3	61	35	203	95	108	133	46	18	28	21	11	5
	2	58	71	2.7	1.4	39	19	166	93	71	112	23	7	16	9	3	—
	3	71	73	6.0	2.8	82	39	129	71	58	77	23	12	11	15	7	4
	4	71	72	3.0	1.9	42	26	140	87	53	100	27	14	13	16	15	8
	5	98	75	4.8	2.8	64	37	178	87	91	116	43	19	24	24	—	7
	M	77	72	4.2	2.2	58	31	163	87	76	108	32	14	18	18	9	6
B 10 min AE	1	75	73	4.5	2.5	62	34	172	76	96	98	39	16	23	22	11	6
	2	71	71	3.1	1.6	44	22	158	84	74	88	23	6	17	7	1	—2
	3	68	73	7.7	3.6	105	50	117	69	48	83	25	10	15	14	7	4
	4	72	72	3.4	2.1	47	29	146	86	60	105	25	12	13	12	15	11
	5	88	75	3.8	2.2	51	30	146	77	69	99	42	19	23	21		9
	M	75	71	4.5	[illegible]	62	33	148	78	69	95	31	13	[illegible]	[illegible]	9	6
A 10 min AE	1	70	70	4.9	2.7	70	38	200	90	110	118	40	15	25	19	–	4
	2	57	71	3.1	1.6	41	22	—	—	—	—	56	16	10			
	3	71	73	11.6	5.5	159	75	103	65	38	77	23	11	12	15		4
	4	72	72	2.9	1.8	40	22	135	84	51	97	27	13	14	17	16	9
	5	91	75	4.4	2.6	59	31	154	82	72	[illegible]	33	[illegible]	20	18	—	1
	M	72	72	[illegible]	2.8	[illegible]	33	[illegible]	80	68	100	[illegible]	11	22	17	9	5

Syst per sec cm	TVR in dyn s cm	CBV in ml	MFT in secs	Left ventricular minute work per sq m BSA	Left ventricular stroke work index per sq m BSA	Right ventricular minute work per sq m BSA	Right ventricular stroke work index per sq m BSA	pH	pO_2 mm Hg	pCO_2 mm Hg	Stand bicarb in mEq/l	Inel tel R/r 100 ml
—	196	1532	19	3 30	41 62	—	—	7 39	63	36	21	62
1340	111	2058	19	4 17	58 18	1 12	15 64	7 34	65	38	19 5	71
64	61	25 8	17	4 62	63 39	0 88	12 04	7 40	74	37	22	30
1217		1625	15	4 5	52 55	—	—	7 49	90	28	21	30
1584	—	1570	16	—	—	1 39	18 55	7 38	69	37	21	04
12.6	123	186	17	4 17	53 95	1 13	1 41	7 0	72	35	21	59
1698	100	1 3	19	4 22	59 84	1 10	15 56	7 42	63	36	22 5	52
1746	148	1690	18	3 86	54 26	0 84	11 89	7 36	67	37	20	50
688	103	2693	16	5 48	74 26	1 04	14 14	7 42	85	37	23	24
1424	58	13 5	15	4 21	53 22	0 51	6 43	7 47	80	32	23	31
1823	—	1 07	16	—	—	1 06	13 99	43	68	35	22	49
1 76	109	181	17	4 4	60 0	0 91	12. 0	42	3	3.	2.	1
1933	167	1433	20	3 10	38 6	0 59	7 34	—	—	—	—	55
2740	1 1	1077	22	1 3	21 5	0 21	2 89	—	—	—	—	56
806	8	2040	17	3 47	4 94	0 46	6 39	—	—	—	—	[illegible]
2131	44	1080	18	2 66	37 52	0 27	3 9	—	—	—	—	30
1615		1200	15	—	—	0 6	10 06	—	—	—	—	69
18	ff	13 6	18	2 7	37 24	0 6	6 11	—	—	—	—	47
22 3	231	1200	16	3 82	58 07	0 59	9 04	—	—	—	—	46
—	1 8	990	22	2 08	28 17	—		—	—	—	—	41
9 2	107	1600	16	2 67	37 13	0 42	5 83	—	—	—	—	20
2451	27	1000	20	2 20	30 06	0 21	2 83	—	—	—	—	28
1815	—	1120	14	—	—	0 65	8 55	—	—	—	—	—
1878	138	118	18	2.69	38.36	0 7	6.56	—	—	—	—	7
1634	195	1425	19	2 96	40 23	0 54	40	42	0	34	21	43
2320	15	1188	23	1 89	26 03	0 20	2 69	7 37	3	39	21	53
820	73	2182	1	3 2	51 63	0 49	6 80	7 41	82	38	23	20
2200		1090	18	2 57	35 50	0 03	0 39	7.53	81	26	22	25
1803	—	10 7	1	—	—	0 45	6 12	7 39	[illegible]	37	21 5	[illegible]
1	141	13 8	18	79	38 36	0 31	4 68	7 42	7	3.	2.	39
1859	196	1388	17	4 08	57 36	0 55	5	40	80	38	22.5	39
		1137	22			—		7 39	5	33	19 5	37
03	69	4180	18	5 39	3 44	0 82	11 22	7 43	86	38	24	18
2425	25	1015	21	1 98	24 24	0 20	2 39	49	81	28	21	27
18 1	—	1100	15			0 50	6 47	7 46	9	35	24	33
166.	93	1674	15	3.8	51 68	0 2	6 96	43	80	3	22	[illegible]

Table E (continued)

	Case	Atrial rate in beats/min	Ventricular rate in beats/min	CO in l/min	CI in l/min	SV in ml	SI in ml	Blood pressure in mm Hg									
								Ascending aorta				Pulmonary artery					
								Systolic	Diastolic	Pulse pressure	Mean	Systolic	Diastolic	Pulse pressure	Mean	[illegible]	[illegible]
B 8 min L	1	120	79	4.9	2.7	62	34	225	73	152	129	79	36	43	51	39	—
	2	102	71	6.5	3.3	92	46	194	77	117	113	61	19	42	29	20	4
	3	96	73	9.1	4.3	125	59	144	74	70	95	43	18	25	23	16	8
	4	97	88	6.5	4.0	74	46	179	97	82	116	—	—	—	—	32	17
	5	136	75	5.7	3.3	76	44	207	93	114	134	73	38	35	52	—	21
	M	110	77	6.5	3.5	86	46	190	83	107	117	64	28	36	39	27	13
A 8 min E	1	120	70	5.6	3.1	80	44	225	76	149	132	67	34	33	39	32	13
	2	81	71	5.4	2.7	76	38	207	90	117	121	58	19	39	26	16	3
	3	88	73	10.1	4.8	138	65	140	64	76	95	43	18	25	24	11	8
	4	85	80	5.5	3.4	69	43	167	87	80	110	42	19	23	23	19	12
	5	122	75	6.4	3.7	85	49	245	145	100	166	69	39	30	41	—	20
	M	99	74	6.6	3.5	90	48	197	92	10[illegible]	125	56	26	30	31	20	11
B 4 min AE	1	80	79	4.3	2.4	54	30	194	86	108	111	49	22	27	25	16	7
	2	75	71	2.8	1.4	39	20	173	93	80	93	14	5	9	8	2	−3
	3	68	73	7.2	3.4	99	47	114	68	46	82	29	8	21	14	7	4
	4	72	72	3.6	2.2	50	31	168	97	71	106	33	15	18	19	17	10
	5	100	75	4.8	2.8	64	37	175	84	91	109	54	26	28	32	—	12
	M	79	74	4.5	2.4	61	33	165	86	79	100	36	15	21	20	11	6
A 4 min AE	1	88	70	4.5	2.3	64	35	203	95	108	133	46	18	28	21	11	5
	2	58	71	2.7	1.4	38	19	166	95	71	112	23	7	16	9	3	—
	3	71	73	6.0	2.8	82	39	129	71	58	77	23	12	11	15	7	4
	4	71	72	3.0	1.9	42	26	140	87	53	100	27	14	13	16	15	8
	5	98	75	4.8	2.8	64	37	178	87	91	116	43	19	24	24	—	7
	M	77	72	4.2	2.2	58	31	163	87	76	108	32	14	10	10	9	6
B 10 min AE	1	75	73	4.5	2.5	62	34	172	76	96	99	39	16	23	22	11	6
	2	71	71	3.1	1.6	44	22	158	84	74	88	23	6	17	7	1	−2
	3	68	73	7.7	3.6	105	50	117	69	48	83	25	10	15	14	7	4
	4	72	72	3.4	2.1	47	29	146	86	60	105	25	12	13	12	15	11
	5	88	75	3.8	2.2	51	30	146	77	69	99	42	19	23	24	—	9
	M	75	73	4.7	2.4	62	33	1[illegible]8	78	69	93	31	13	[illegible]	16	9	6
A 10 min AE	1	70	70	4.9	2.7	70	38	200	90	110	118	40	15	25	10	7	4
	2	57	71	3.1	1.6	44	22	—	—	—	—	56	16	40			—
	3	71	73	11.6	5.5	159	75	103	65	38	77	23	11	12	15	5	4
	4	72	72	2.9	1.8	40	22	135	84	51	97	27	13	14	17	16	9
	5	91	75	4.4	2.6	59	31	154	82	72	107	33	13	20	18	—	4
	M	72	72	5.4	2.8	7[illegible]	3[illegible]	1[illegible]8	80	68	100	36	1[illegible]	22	17	9	5

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DEPARTMENT OF RADIOTHERAPY LASARETTET LUND AND
DEPARTMENT OF INTERNAL MEDICINE, CENTRALLASARETTET KALMAR, SWEDEN

ON CHROMOPHOBE PITUITARY ADENOMA

A REVIEW OF 131 CASES

BY

ESKIL FÜRST

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MALMÖ
SYDSVENSKA DAGBLADETS AKTIEBOLAG
1966

To my wife and family

CONTENTS

INTRODUCTION

SCHÖNEMANN (1892) must be given credit for our fundamental knowledge of the histological characters of the pituitary. He showed that the gland is built up of three types of cells which are called chromophobe, acidophil and basophil according to their stainability. BENDA (1900) classified pituitary tumours according to the predominant type of cells as chromophobe, acidophil and basophil adenomas.

In large neurosurgical series pituitary adenoma represents 6.2 to 17.8 % of all brain tumours (HENDERSON 1939, GRANT 1948, BAKAY 1950, YOUNGHUSBAND ET AL. 1952) and the chromophobe adenoma 76.9 to 86.6 % of all pituitary adenomas in these series.

PIERRE MARIE (1886) was the first to report a relation between acromegaly and pituitary tumour. DOTT & BAILEY (1925), who studied Cushing's series of pituitary tumours, demonstrated a relationship between the histopathology of the tumours and a pituitary hormonal activity. It has since been generally thought that acromegaly is due to acidophil pituitary adenoma and that some cases of Cushing's syndrome are due to proliferation of endocrine active basophil cells. Pituitary tumours built up of chromophobe cells should not, on the contrary, cause pituitary hyperfunction but often insufficiency of one or more target organs (gonads, thyroid and adrenal cortex). Chromophobe pituitary cells were therefore thought to be hormonally inactive.

DOTT & BAILEY (1925) found some chromophobe adenomas to contain a minor portion of sparsely granulated acidophil cells and called these adenomas "mixed adenomas". BAILEY & CUSHING (1928) pointed out that adenomas with this type of histological picture occurred in patients who had not only insufficiency of the target organs but also slight signs of acromegaly. This clinical picture was called "fugitive acromegaly". The relationship between this specific granulation and endocrine activity has been thought to be confirmed in later works by TÖNNIS, MÜLLER & BRILMAYER (1953), BRILMAYER, MARGUTH & MÜLLER (1957) and RUSSFIELD, REINER & KLAUS (1956).

In recent years, however, it has been shown that the correlation between the histological picture and the clinical picture is not so close as formerly

supposed Thus, some patients with acromegaly have been found to have a purely chromophobe adenoma (ANGELSTEIN 1953, HEIMBACH 1959), and a fairly large number of cases of Cushing's syndrome with chromophobe pituitary tumours have been described (PLOTZ, KNOWLTON & RAGAN 1952, NELSON ET AL 1958, MARKS 1959, SALASSA ET AL 1959, NELSON ET AL 1960, ROVIT & BERRY 1965)

In most large clinical series the patients have been classified according to the histological picture of the pituitary tumours Consequently cases of acromegaly (HEIMBACH 1959) and of Cushing's syndrome (MOGENSEN 1957) have been included in follow-up studies of patients with chromophobe pituitary adenoma Many of these large series of chromophobe adenoma have included a number of cases with mixed adenomas and signs of "fugitive acromegaly" (HENDERSON 1939, YOUNGHUSBAND ET AL 1952, NURNBERGER & KOREY 1953, HEIMBACH 1959)

In the majority of published cases of pituitary tumour the specimens examined were obtained at operation It is well known that such operations are rarely radical and that at least the major part of the capsule of the adenoma must be left behind Besides this, the tissue removed will with but few exceptions represent only a small part of the entire adenoma This may help to explain the discrepancy sometimes found between the histological picture and the clinical course

On the other hand, in the investigations of adenoma from patients with acromegaly SCHELIN (1962) found cells which when examined under the light microscope appeared to be chromophobe, but which on examination in the electron microscope proved to be sparsely granulated acidophils with signs of active secretory function SCHELIN therefore claimed that it is not always possible to demonstrate or exclude secretory function of the cells under the light microscope

The term chromophobe adenoma is now used to designate a clinical picture due to an expanding tumour originating from the anterior lobe of the pituitary and without signs of hormonal overactivity It would therefore appear reasonable to accept this definition and, in contrast to what was previously the rule, not to classify the patients according to the histological features

Those authors, usually neurosurgeons, who were the first to focus interest on the clinical features of chromophobe adenoma, naturally directed their attention mainly to the neurological, and particularly neuro-ophthalmological, symptoms HENDERSON (1939) thus thoroughly investigated the various types of visual field reduction in chromophobe adenoma and studied the effect of operation on those defects

As mentioned above, chromophobe pituitary adenoma can cause a partial or complete loss of pituitary function with symptoms of insufficiency of the target organs Such symptoms can also be produced by treatment given The endocrinological picture of chromophobe pituitary adenoma before treatment has been discussed on the basis of large

series by YOUNGHUSBAND ET AL. (1952), NURNBERGER & KOREY (1953), OBERDISSE (1957). The occurrence of adrenocortical insufficiency has also been thoroughly discussed by RUHSTRAT (1960) on the basis of a series of 53 operated cases. FISCHER (1963) reported an endocrinological and psychiatric re-examination of 75 patients operated upon for chromophobe adenoma. Only one follow up study with chromophobe pituitary adenoma has been published with special reference to the endocrine disturbances before and after treatment (MOGENSEN 1957).

It is difficult to evaluate the results of some of these re-examinations owing to the crudity of the methods employed at that time for assessing endocrine function. Several authors only reported the occurrence of certain symptoms and the result of certain clinical function tests, but they gave no comprehensive description of the function of the target organs in the individual cases and did not say anything about the frequency of target gland insufficiencies.

The principles of treatment of pituitary adenoma have been the subject of much debate since the beginning of the century. Operations to decompress the optic nerve were tried early. CUSHING and his co-workers were pioneers in this field (CUSHING 1912, 1933, HENDERSON 1939). The pros and cons of various surgical techniques have been discussed. Most neurosurgeons, however, prefer the transfrontal approach (HENDERSON 1939, BAKAY 1950, TONNIS, OBERDISSE & WEBER 1954, HEIMBACH 1959), others the transsphenoidal approach (HIRSCH 1959, GUIOT & THIBAUT 1959).

On the basis of experience gained in CUSHING's series of patients with pituitary adenoma HENDERSON pointed out as early as 1939 that roentgen treatment after surgical decompression diminished the risk for recurrence of tumour. Especially after improvement of the radiation technique CUSHING's former pupil, HORRAX, recommended primary radiation treatment in all cases with slight to moderate disturbance of vision because it often brought about effective decompression of the optic nerve and relief of the symptoms (HORRAX ET AL. 1952, HORRAX 1958, POPPEN 1963).

ARNOLD's (1954) experiment with irradiation of the pituitary in monkey and a few clinical observations (HEIMBACH 1959, DECKER & LAUTER 1960, CROMPTON & LAYTON 1961, ALMQUIST ET AL. 1964) however suggested that at least occasionally such therapeutic radiation can interfere with the hypothalamic-hypophyseal function. These and similar observations appeared to induce at least some neurosurgeons not to refer their patients for postoperative roentgen therapy (TONNIS, OBERDISSE & WEBER 1954, MOGENSEN 1957, MARGUTH (1959).

Investigation of side-effects of irradiation of the pituitary for any variation of the technique and dose used is desirable. A further point requiring investigation is in what extent postoperative radiotherapy can reduce the incidence of recurrences.

It is obvious from previous series on record that a fair number of patients

have for many years had a tumour and repeatedly sought medical advice without the cause of their symptoms being diagnosed. It was therefore thought worthwhile investigating which symptoms induce the patient to consult a doctor and which symptoms are the first to direct the examinor's thoughts to the possibility of a pituitary tumour.

At Lasarettet, Lund, a large number of patients with chromophobe pituitary adenoma have been examined and treated since 1921. In 1946 a department of neurosurgery was set up at the hospital, where most patients with pituitary adenoma have since been operated upon. Since that year pituitary tumours have been treated according to uniform principles at the department of radiotherapy. In a large proportion of the patients combined treatment with operation and postoperative radiotherapy was used. From 1954 patients with pituitary tumours have been endocrinologically investigated before and after treatment according to fairly uniform principles at the department of internal medicine. These patients with chromophobe pituitary adenoma have been followed up at the above departments.

While serving at the medical clinic A in Lund from 1953—1959, the present writer took part in the examination of these patients and had the opportunity of carrying out a follow-up study of the entire series from 1921—1960. This series consists of 131 patients, 80 of whom were re-examined by the writer personally.

It was on the basis of this material that the present investigation was started with the purpose of

1. elucidating the development of the anamnestic symptoms of chromophobe adenoma,
2. describing and discussing the treatment given in the present series,
3. analysing the clinical findings, with special reference to visual disturbances, radiologic changes and endocrine disturbances before and after primary tumour treatment, and
4. analysing the results of treatment with reference to operative mortality, recurrences and survival and to the working capacity of the patients.

CHAPTER 1

MATERIAL AND METHODS

Perusal of the case records at the departments of internal medicine, neurosurgery and radiotherapy Lasarettet, Lund revealed that from 1921—1960 chromophobe pituitary adenoma had been diagnosed in all together 136 patients In 5 of these cases treated in 1926 1930 1947, 1953 and 1955, however the notes in the records were not complete enough for the diagnosis to be accepted as firm The records of the remaining 131 cases were analysed to check the diagnosis according to certain criteria which will be described here

The roentgenologists reports accompanying these case records as well as the roentgenograms available in most of the cases invariably contained notes respectively signs of an intrasellar expanding process with or without suprasellar extension

The case records also included photographs of 100 of the patients Judging from these photographs and from the mostly detailed descriptions of the patients none of the patients had signs of acromegaly Neither had they exhibited symptoms or signs of Cushing's syndrome

One hundred and ten patients had been operated upon and 1, who had been treated with radiation only, had been examined at necropsy In all these 111 cases the diagnosis of pituitary tumour was confirmed histologically In 95 the specimen consisted entirely of chromophobe cells while in 16 it also contained sparse acidophil cells

Histological material from 98 cases was still available Re-examination of this material in 1963 confirmed the correctness of the diagnosis in all 98 cases [1]

Table 15 in the Appendix gives data about the 131 patients of the present series Hereinafter patients will be referred to in the text by the number allotted them in this table

Fig 1 shows the distribution of the patients over the 40-year period 1921—1960 The marked increase in 1946 can be explained by the fact that the department of neurosurgery was opened that year

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[1] I wish to thank Dr G Skold and Prosector N O Berg Institute of Pathology Lund for generous help with the re-examination of the histological material.

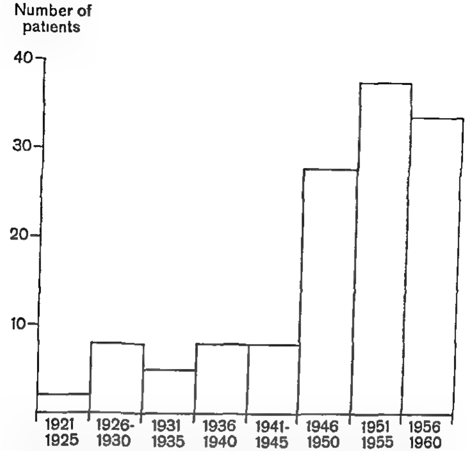

Fig 1 *One hundred and thirty one patients with chromophobe pituitary adenoma distributed among 5 year periods between 1921 and 1960 at the University Hospital Lund*

Fig 2 gives the age- and sex-distribution (53 females and 78 males) At the time of diagnosis 68 % of the females and 78 % of the males were 40 to 69 years old The mean age of the females was 46 years (range 17—70) and for the males 49 years (range 14—74)

Data about the 131 patients were obtained mainly from the archives of Lasarettet, Lund Information was also procured from the case records of the department of neurosurgery, Serafimer-*lasarettet*, Stockholm, concerning 16 patients operated upon there before 1946 The patients' records at local hospitals were also studied [1]

The clinical re examination of the patients was carried out during 1960—1961 Fifty-one of the patients had died before the re-examination

Of the 80 patients still living in 1960—1961, all were examined by the author For this purpose 63 of them were

[1] I beg to thank Prof H Olivecrona department of neurosurgery Serafimerlasarettet Stockholm Prof L Leksell former chief of clinic A department of neurosurgery Lasarettet Lund and Prof J Waldenstrom medical clinic Malmo general hospital Malmo for generous access to their archives as well as all colleagues who have helped me to collect the material

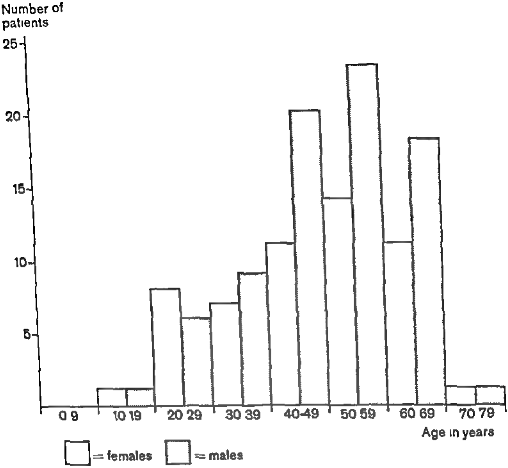

Fig 2 *Age distribution in 53 female and 78 male patients with chromophobe pituitary adenoma at the time of diagnosis*

admitted to Lasarettet, Lund and 6 to the department of internal medicine Lasarettet Kalmar and 1 to the department of internal medicine, Lasarettet, Vastervik Eight patients were examined at the outpatient departments by the author Two women (Nos 38 and 84) who were not willing to go to the hospital were re-examined at their homes Examination of these 2 patients included a supplementary inquiry into their history

In the calculation of the survival time the series was followed up until the end of 1965

The investigation aimed at obtaining satisfactory all round information on the patients with special reference to the occurrence of signs of recurrence and the state of the target glands (gonads,

thyroid and adrenal cortex) All 78 patients re-examined at hospital were examined ophthalmoneurologically, besides which roentgenograms were taken of the sella turcica All 70 patients admitted to hospital *for re-examination* were investigated endocrinologically according to a special plan described in detail in Chapter VI

COMMENTS

The purpose of the re-examination was to study a group of patients in whom the diagnosis of chromophobe pituitary adenoma by conventional clinical criteria could be accepted as firm The re-examination *revealed that roentgenological* signs of pituitary tumour had been demonstrated in 131 cases In 111 cases tumour tissue removed at operation or necropsy had been examined histologically *In all these cases the tumour had* proved to be built up of tissue originating from the anterior lobe and showing no signs of malignancy In the remaining 20 cases the diagnosis had not been confirmed histologically *The diagnosis of* these 20 cases therefore will be discussed separately The symptoms, clinical findings and course of the disease, however, did not argue against the diagnosis

Other expanding tumours, *such as* craniopharyngioma and suprasellar meningioma can *sometimes* not be differentiated roentgenologically or opthalmoneurologically from pituitary adenoma These expanding tumours, *especially* craniopharyngioma, can produce a clinical picture with symptoms of pituitary insufficiency of the type seen in chromophobe pituitary adenoma (KAHANA ET AL 1962) But these tumours differ essentially from pituitary adenomas in respect of the results of surgical as well as radiation therapy (MULLER & WOHLFART 1950, WISE ET AL 1955, JEFFERSON 1957, WHITE 1964 and others)

Of the 20 patients in whom the diagnosis had not been verified at operation, 17 had shown suprasellar extension of the tumour with symptoms and signs of compression of the optic nerve In all of these cases the visual disturbances regressed after roentgen treatment The tumours must thus have been radiosensitive and this lends support to the diagnosis of pituitary adenoma (NURNBERGER & KOREY *1953) Three of* the 20 patients had no ophthalmoneurological symptoms or signs These patients had also received roentgen therapy, after which the tumours had *showed no signs of further growth for* the following 7—10 years, during which they were followed up Though the differentiation of these 3 last-mentioned cases from slow growing craniopharyng*ioma or possibly meningioma cannot* be regarded as established with absolute certainty, the diagnosis does appear firm enough to justify their inclusion in the present series

As to the clinical picture the entire material appears to be uniform in so far as none of the patients have had signs of hyperfunction of the pituitary, while most of them exhibited evidence of *pituitary insufficiency* In 16 cases the histological examination had shown "mixed type adenomas but none of these patients had signs of acromegaly

either. Cases with signs of pituitary hyperactivity have been included in a large number of series described by neurosurgeons (HENDERSON 1939, YOUNGHUSBAND ET AL. 1952, NURNBERGER & KOREY 1953, MOGENSEN 1957 and HEIMBACH 1959). It would appear advantageous to use clinical criteria in the diagnosis of chromophobe adenoma as in the present investigation. As pointed out in the introduction the specimens of the tumours removed at operation and examined histologically are only rarely representative of the entire tumour. The relationship between cellular picture and secretory activity is still obscure (SCHELIN 1962, ROVIT & BERRY 1965).

Of the present material 40 % were women and 60 % were men. This preponderance of men was probably due to chance since in other large series on record the disease was roughly equally common in both sexes (YOUNGHUSBAND ET AL. 1952, NURNBERGER & KOREY 1953, WISE ET AL. 1955, KERNOHAN & SAYRE 1956, JEFFERSON 1957, ANDERSSON 1957, HEIMBACH 1959).

The average age of the patients at the time of the diagnosis in the present material was 48 years in both males and females which is roughly the same as that found in other large series (HENDERSON 1939, KERNOHAN & SAYRE 1956, JEFFERSON 1957 and others).

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Table 1 *Occurrence of symptoms in 131 patients with chromophobe pituitary adenoma at the time of diagnosis*

Symptoms	Incidence Number	Total studied	Per cent
Visual disturbances	117	131	89
Headache	71	131	54
Epileptic seizures	4	131	3
Polydipsia and polyuria	3	131	2
Menstrual disturbances and amenorrhoea	28	35	80 } 68
Libido and or potency reduced	31	52	60 }
Sex hair growth reduced { females	13	42	38
Sex hair growth reduced { males	29	70	
Cold intolerance	21	86	24
Tiredness and weakness	34	131	26
No symptoms (accidental diagnosis)	1	131	1

in the Appendix The frequencies of the various symptoms are given in Table 1 Some of the symptoms discussed here had not been noted in the records of the patients treated in the beginning of the period covered by the present investigation This received due consideration in the calculation of the frequencies of the various symptoms

VISUAL DISTURBANCES (V)[1]—At the time of the diagnosis 117 (89 %) of the 131 patients had some form of visual disturbance One hundred and four patients had noticed impairment of visual acuity which was one sided in 40 of them Visual field defects besides loss of visual acuity had been noted in 23 cases Double vision permanent or periodical had been noted in 23 cases Fourteen had not noticed any visual disturbances

HEADACHE (H) —Seventy one (54 %) of the 131 patients had headache It was fronto temporal in 14 while in 18 it was unilateral and localised to the orbital region In 6 cases it was occipital or parietal In 33 patients the region of the headache had not been noted In 12 cases the headache was fairly mild and had appeared only a short time before the diagnosis had been made In 21 cases it was severe and often periodic and associated with dizziness and nausea. One woman (No 76) had had headache and impaired vision during menstruation In 2 cases (Nos 64 and 127) the patients had had severe attacks of headache besides impairment of hearing and in these a presumptive diagnosis of Meniere s disease had been made but the further course had directed the examiner s attention to the pituitary tumour In 4 cases (Nos 58, 74 81 and 111) the headache disappeared as the visual disturbances supervened

EPILEPSY (E) —Four patients had a history of epilepsy One patient (No 6) initially had visual symptoms followed by generalised convulsions In the other 3 patients (Nos 15 26 and 48) the attacks had begun with paresthesia and twitches in one half of the face or in the jaws followed by loss of consciousness

[1] The symbols given in brackets are the same as those used in Table 15 in the Appendix

CHAPTER II

ANAMNESTIC SYMPTOMS

The anamnestic symptoms of chromophobe pituitary adenoma are sometimes very complex. The growing tumour can produce a number of diffuse symptoms suggesting intracranial expansive process, *e.g.*, headache with or without dizziness and vomiting. The tumour may also produce symptoms of local pressure on the optic nerves and the chiasma. Finally, pressure on the pituitary can cause symptoms of insufficiency of the peripheral endocrine organs governed by the anterior lobe of the pituitary and sometimes, though rarely, it can cause functional disturbances of the posterior lobe.

An early diagnosis requires knowledge of the details of the complex clinical picture. If the tumour is not detected in time, there is a risk of permanent injury to the optic nerve. An early diagnosis is also important in order to allow adequate treatment before the tumour has had time to produce irreversible damage with impairment of the function of the pituitary. The various symptoms are often unspecific, but they often occur in certain combinations with one another and sometimes with more specific symptoms. It is known from previous investigations that the patients often have symptoms a long time before they consult a physician and, secondly, that the tumour may remain unrecognised for a long time even in patients who do consult a physician early and repeatedly for obvious symptoms of the disease.

It was therefore thought desirable and legitimate to elucidate the anamnestic symptoms and development of the picture of symptoms which finally led to the diagnosis in the present series.

At the present re-examination in 1960—1961 anamnestic data about most of the 80 patients still living could be checked and often supplemented. It should, however, be stressed that the anamnestic symptoms described here and forming the basis of the diagnosis were mainly primary anamnestic data extracted from the hospital case records, since the re-examination was often not performed until several years after the patient had been treated. The presentation is limited to a description of the incidence of certain well known and characteristic symptoms. The symptoms noted in the individual cases are given in Table 15.

the 34 patients had more or less acquiesced in their condition Because of this frequently pronounced mental sluggishness many had not sought medical advice until they had been forced to by their relatives (Nos 22, 32, 40, 41, 42, 55 72 and 83) In the older patients the relatives had often thought that the symptoms were signs of old age, and medical consultation was therefore postponed until impairment of vision had become severe In some of the patients periods of drowsiness and stupor occurred, often in association with the above mentioned episodes of headache, nausea and vomiting For a few years before the diagnosis 2 men (Nos 32 and 41) had not only the symptoms described above but also impotence and cold intolerance as well as painful cramps of the lower limbs and pronounced rigidity In 20 of these 34 cases there were symptoms suggesting simultaneous gonadal insufficiency or hypothyroidism In some of the cases, however there were no certain signs of target gland insufficiency but pronounced mental sluggishness and markedly decreased visual acuity (*e g*, cases 12 13, 21 42 50 55 72, 74 and 109)

In 1 patient (No 91) the condition was *incidentally diagnosed* at roentgen examination of the skull because of head injury At the time the patient had no symptoms of adenoma

INITIAL SYMPTOMS AND DEVELOPMENT OF THE PICTURE OF SYMPTOMS

One might imagine that those patients in whom the disease was ushered in by ophthalmoneurological symptoms would because of the dramatic onset, soon seek medical advice This might also hold for those cases in which the disease had started with severe headache and dizziness One might also expect that the interval between the onset and the diagnosis would be longer in those patients in whom the onset was characterised by endocrine insufficiency, because these symptoms are often diffuse or difficult to interpret In chromophobe pituitary adenoma as in many other diseases, the interval between the onset of symptoms and the diagnosis depends on a wide variety of factors including the insight of the patients and their relatives and socioeconomic standard Finally, it is not always possible to make an early diagnosis of chromophobe adenoma *e g*, in those cases in which the initial symptom is amenorrhoea and the tumour is still small and intrasellar

It proved impossible to recognise any systematic sequence of development of the symptoms of the chromophobe pituitary adenoma The course in a given case is influenced by too many widely different factors Since space would not allow a detailed account of all the cases in the present series it was decided to assign the patients to various larger groups according to the initial symptoms or certain combinations of symptoms

The duration given for the individual symptoms which form the basis of the analysis is deduced by the author from notes made in the hospital records and interviews with the patients and it is in some cases uncertain

and convulsions in one half of the body or generalised

POLYDIPSIA AND POLYURIA (P) —One patient (No 45) had polydipsia and polyuria for about half a year These symptoms disappeared about a couple of months before the diagnosis had been made Two women (Nos 90 and 129), in whom the disease made its first appearance during the last pregnancy, had increased thirst and passed large amounts of urine during the last months of pregnancy The urine output was 5—8 litres a day During that period vision was also severely impaired

MENSTRUAL DISTURBANCES AND AMENORRHOEA (G) —Menstrual disturbances or amenorrhoea had been reported by 28 (80 %) of 35 women in premenopausal age In 6 of these patients it is doubtful, however, whether any causal relationship existed between the menstrual disorders and pituitary tumours Four women had after a period of irregular menstruations followed by amenorrhoea undergone hysterectomy In 2 of them (Nos 28 and 76) laparotomy had revealed large cystic ovaries, while in 2 (Nos 69 and 127) operation had been performed but the diagnosis had not been entered in the records Two patients (Nos 47 and 105) had never menstruated, one (No 105) of them being a case of classical Turner's syndrome

LIBIDO AND/OR POTENCY REDUCED (G) —In 31 (60 %) of 52 men libido and potency had been reduced Some of them had reported only a slight reduction, but most of them total loss of potency

SEX HAIR GROWTH REDUCED (S) —Thirteen out of 42 women and 29 men out of 70 had themselves observed reduction or loss of sex hair growth In most of the men growth of the beard had got so reduced that they only had to shave once a week The patients usually observed simultaneous reduction of axillary and pubic hair growth

Five women and twelve men reported that they had only sparse hair growth ever since puberty It is uncertain whether the reduced hair growth in these cases had anything to do with the pituitary tumour

COLD INTOLERANCE (C) —Sensitivity to cold, particularly of the hands and feet, and intolerance to rapid changes in temperature were reported by 21 (24 %) of 86 patients in whom data were available Only in 6 of these 21 patients had constipation been noted

TIREDNESS AND WEAKNESS (T) —Besides the above-mentioned and fairly well defined symptoms tiredness and weakness, usually together with other diffuse symptoms, were noted Such symptoms were noted in 34 (26 %) of 131 patients together with one or more of the previously described symptoms Since most of the patients had a complex of fairly unspecific symptoms, it was decided to try to describe the clinical picture instead of the individual symptoms separately

In most of these 34 patients the picture was dominated by tiredness and weakness with consequent impairment of working capacity Many of the patients or their relatives reported increasing lack of initiative About half of

sufficiency at the time of diagnosis The duration of the visual disturbances was 2 years (range 1—5 years) in 14 of them One patient (No 85) had had unilateral impairment of vision for 24 years and headache associated with impotency for 10—15 years, before he sought medical advice because of impairment of vision of the other eye, too In 3 (Nos 45, 90 and 129) of these 15 patients visual disorders occurred in combination with polydipsia and polyuria, and in the other cases symptoms of disturbed gonadal function and/or other symptoms of endocrine insufficiency supervened

In 18 patients the first symptom was *headache* on the average for 5 years before the diagnosis was made (4 months —28 years) Headache was the only symptom in 1 patient (No 117) for 4 months before the diagnosis was incidentally made at examination for allergic rhinitis In 1 patient (No 48) the right eye had been enucleated at 15 years of age because of microophthalmia Already before that time the patient had had attacks of migraine like headache From 30 years of age on she had periodically had severe headache behind the right orbit Her tumour remained undiagnosed despite medical examination For almost 1 year before the diagnosis she was then 58 years of age vision on the left side began to fail and epileptic attacks began to appear These manifestations led to the diagnosis A large pituitary adenoma had developed below the optic nerve of the enucleated eye

In 11 of these 18 patients supervention of visual disturbances during the last year before the diagnosis led to the discovery of the disease One of them (No 127) had had typical attacks of Meniere's syndrome, but she had also had headache of fairly constant character for 6 years before the diagnosis The patient consulted her physician for the headache, but no explanation could be found for it until visual disturbances supervened

In 5 of the 18 patients in whom the initial symptom was headache, symptoms of gonadal insufficiency, severe tiredness and lack of initiative appeared shortly before the diagnosis was made One (No 75) of these 5 patients had had headache for 10 years, the others for 1—4 years In 3 of these cases it was apparently the rapid impairment of vision that had led to the diagnosis

Initial symptoms of *target gland insufficiency*, mainly gonadal insufficiency occurred in 57 patients, on the average 7 years before the diagnosis

In 4 (Nos 41 70 10. and 115) of the 57 patients the only symptoms were those of endocrine insufficiency for 10—13 years before the diagnosis Patient No 41 repeatedly sought medical advice and had been admitted to a department of internal medicine because of pronounced weakness and intolerance to cold His symptoms had been interpreted as mild anaemia and primary hypothyroidism but replacement treatment had *no effect* and *the correct diagnosis* was *not* made until 6 years after the primary medical examination Patient No 70 attended her doctor for several years for amenorrhoea followed by weakness and intolerance to cold symptoms which were interpreted as signs of pituitary in

Table 2 *Initial symptoms in 131 patients with chromophobe pituitary adenoma*

Symptoms	Number of patients
Visual disturbances	54
Headache	18
Epileptic seizures	1
Menstrual disturbances amenorrhoea	23
Libido and/or potency reduced	20
Tiredness and weakness	14
No symptoms (accidental diagnosis)	1
Total	131

INITIAL SYMPTOMS—The distribution of the initial symptoms is given in Table 2 In 73 (56 %) cases the first symptom of the disease was neurological, with visual disturbances in 54 cases, headache in 18 and with epilepsy in 1 Symptoms of endocrine insufficiency were the initial ones in 57 (44 %) patients, with symptoms suggesting gonadal insufficiency in 23 women and 20 men, *i e*, one third of the 131 patients In 14 patients the initial symptoms were tiredness, lack of initiative and intolerance to cold, which may be interpreted as signs of endocrine insufficiency

DEVELOPMENT OF SYMPTOMS —Generally speaking, those patients, in whom the disease was not diagnosed until long after the onset, had a single symptom for many years, after which other symptoms appeared fairly soon after one another with subsequent recognition of the disease

Of the 54 patients in whom *visual disturbances* were the first symptoms observed, the patients had had these symptoms for, on the average, 3 years (3 months—24 years) In 24 patients these were the only symptoms before the diagnosis was made Twenty-two of these 24 patients had had visual disturbances for, on the average, 1 year (2 months—2 years) before the diagnosis The other 2 patients (Nos 79 and 130) had such symptoms for 14 respectively 6 years before the diagnosis One of them (No 79) had anisometropia The ophthalmoneurological picture had been misinterpreted for many years The second patient (No 130) had unilateral impairment of vision for a long time before he sought medical advice because of impairment of vision also on the other side

In 15 of the 54 patients headache supervened after the onset of the initial visual disturbances In these cases the diagnosis was also made relatively early, on the average within 1 5 years of onset Four patients (Nos 4, 8, 46 and 106) had, however, repeatedly consulted their physician because of various visual disturbances and headache, but the diagnosis of pituitary tumour was not made until after 5—14 years In at least 2 of these cases this delay was due to the fact that the visual disturbances were atypical (periodic attacks of double vision with dizziness and headache, respectively homonymous scotoma)

Of the 54 patients in whom the initial symptoms were visual disorders, 15 had co-existing symptoms of endocrine in

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In 18 patients the first symptom was *headache*, on the average for 5 years before the diagnosis was made (4 months —28 years) Headache was the only symptom in 1 patient (No 117) for 4 months before the diagnosis was incidentally made at examination for allergic rhinitis In 1 patient (No 48) the right eye had been enucleated at 15 years of age because of microophthalmia Already before that time the patient had had attacks of migraine like headache From 30 years of age on she had periodically had severe headache behind the right orbit Her tumour remained undiagnosed despite medical examination For almost 1 year before the diagnosis, she was then 58 years of age vision on the left side began to fail and epileptic attacks began to appear These manifestations led to the diagnosis A large pituitary adenoma had developed below the optic nerve of the enucleated eye

In 11 of these 18 patients supervention of visual disturbances during the last year before the diagnosis led to the discovery of the disease One of them (No 127) had had typical attacks of Menière s syndrome but she had also had headache of fairly constant character for 6 years before the diagnosis The patient consulted her physician for the headache, but no explanation could be found for it until visual disturbances supervened

In 5 of the 18 patients in whom the initial symptom was headache symptoms of gonadal insufficiency, severe tiredness and lack of initiative appeared shortly before the diagnosis was made One (No 75) of these 5 patients had had headache for 10 years the others for 1—4 years In 3 of these cases it was apparently the rapid impairment of vision that had led to the diagnosis

Initial symptoms of *target gland insufficiency* mainly gonadal insufficiency, occurred in 57 patient on the average 7 years before the diagnosis

In 4 (Nos 41 70, 102 and 115) of the 57 patients the only symptoms were those of endocrine insufficiency for 10—13 years before the diagnosis Patient No 41 repeatedly sought medical advice and had been admitted to a department of internal medicine because of pronounced weakness and intolerance to cold His symptoms had been interpreted as mild anaemia and primary hypothyroidism but replacement treatment had no effect and the correct diagnosis was not made until 6 years after the primary medical examination Patient No 70 attended her doctor for several years for amenorrhoea followed by weakness and intolerance to cold symptoms which were interpreted as signs of pituitary in

sufficiency The other 2 patients, who had been impotent for 10—13 years, *complained of marked* supervening weakness and intolerance to cold, and it was these symptoms that induced them to seek medical advice In one (No 115) of them primary hypothyroidism was first suspected until the patient reported that he had been impotent for about 10 years, which led to the diagnosis

In 6 patients the initial symptoms of endocrine insufficiency were later followed by headache Two women (Nos 47 and 82) had amenorrhoea for 10 and 14 years, respectively, until headache supervened, causing them to seek medical advice The other 4 patients (Nos 19, 55, 92 and 118) had also other symptoms of target gland insufficiency, rather soon combined with headache This complex picture of symptoms led to diagnosis within 2 to 5 years

In 47 of the 57 patients in whom the initial symptoms were those of endocrine insufficiency, visual disorders only (26 cases) or these symptoms accompanied by headache (21 cases) later supervened In most of the cases these symptoms appeared in a rather short time and thus soon led to diagnosis

In 9 of the above-mentioned 26 patients visual disturbances were preceded also by further symptoms of endocrine insufficiency than those already existing Five (Nos 23, 40, 83, 120 and 122) of them had sought medical advice repeatedly for 3—7 years, but the disease had not been recognised despite severe symptoms of pituitary insufficiency One patient (No 120) had thus first visited her doctor at 18 years of age because of 1 year's amenorrhoea and she was unsuccessfully treated for a long time with gonadotrophin stimulation and later with thyroid and iron preparations The tumour was not diagnosed until 5 years later, after reduction of the visual fields had supervened, which was also initially misinterpreted because it was atypical In the other 4 (Nos 23, 40, 83 and 122) patients the symptoms were *thought to be due mainly* to anaemia and primary hypothyroidism They had been treated without success with iron and liver preparations, tonics, and thyroid preparations until the appearance of visual disturbances, which led to the diagnosis of the tumour

Another patient (No 126) had amenorrhoea for 28 years before the diagnosis, and visual disturbances for 10 years During these 10 years the patient repeatedly sought medical advice but the nature of her disease was not realised until after supervention of tiredness, intolerance to cold and mental sluggishness

It was impressing that as many as 24 patients had only symptoms of endocrine insufficiency for 6—25 years until the last year before the diagnosis was made Thus there were 10 women with amenorrhoea and 10 men with impotency and 4 patients (Nos 40, 42, 67 and 122) with several more or less marked symptoms, such as increasing fatigue, intolerance to cold and impotency, as the only symptoms until the acute onset of visual disturbances which soon led to diagnosis

Table 3 *Single or multiple symptoms in 131 patients at time of diagnosis of chromophobe pituitary adenoma*

Symptoms	Number of patients
Visual disturbances	25
Visual disturbances + headache	27
Visual disturbances + headache + endocrine symptoms	35
Visual disturbances + endocrine symptoms	32
Headache + endocrine symptoms	8
Endocrine symptoms	4
Headache	1
No symptoms accidental diagnosis	1
	Total 131

ANAMNESTIC SYMPTOMS AT THE TIME OF DIAGNOSIS — It is clear from the preceding section that a wide variety of complexes of anamnestic symptoms had developed before the diagnosis had been made in the 131 cases (Table 3) Anamnestic *visual disturbances were the only symptoms* in 25 cases In all together 94 patients the visual disturbances were associated with other symptoms Thus, 27 patients including 4 who also had epileptic attacks had visual disturbances and headache with or without dizziness and vomiting In 35 patients visual disturbances were associated with headache and with more or less severe symptoms of endocrine insufficiency Visual disturbances combined with symptoms of endocrine insufficiency occurred in 32 cases In 8 cases the records contained notes of headache in combination with endocrine symptoms In 4 cases the records contained notes of endocrine symptoms only One patient in whom the diagnosis was made incidentally had no symptoms of the adenoma

DISCUSSION

The purpose of the investigation of the anamnestic symptoms and their development in the present series of chromophobe pituitary adenomas was set forth on page 16 In view of the rapidly increasing general standard of living in Sweden together with the medical facilities now offered by the Swedish national health scheme, it seems reasonable to assume that a larger number of patients with chromophobe pituitary adenoma will be seen in an earlier stage Wider and more detailed knowledge of the symptom complex would probably also help to increase the frequency of an early diagnosis This would in turn result in a larger percentage of patients with chromophobe pituitary adenoma being able to receive adequate treatment early before the disabling visual disturbances have had time to develop

The difficulty in making an early diagnosis of chromophobe pituitary adenoma has been stressed by various authors (WHITTAKER & WHITEHEAD 1954, OBERDISSE 1957) According to OBERDISSE, this is because the patients often wait so long before they consult a doctor and secondly, because the clinical picture is often misinterpreted. OBERDISSE drew attention to the high frequency of severe visual disturbances in OLIVECRONA'S and TÖNNIS series (BAKAY 1950, TÖNNIS OBERDISSE &

WEBER 1954) as an illustrative example of the dire consequences of delayed diagnosis

The development of the symptom complex before the disease is diagnosed in the present series is, generally speaking, the same as that found by previous workers in this field

Thus, visual disturbances had been noted with equal frequency in BARRET'S (1953), POPPEN'S (1963) and in the present series, i e, about 90 % At the time of the diagnosis as many as one third of the patients in the present material had noticed unilateral impairment of vision When the onset was incipient and progress slow, many of the patients belittled the symptoms and did not trouble to consult their doctor about it This attitude of the patients has been reported in other series (HENDERSON 1939, CHAMLIN & DAVIDOFF 1955, HEIMBACH 1959, NOVER 1962) Double vision was also a strikingly common symptom in the present series WISE ET AL (1955) and JEFFERSON (1957) found that double vision could rarely be recorded objectively, but at the same time stressed that it was disturbing to the patient, and that it indicated thorough ophthalmoneurologic examination

Analysis of the case records showed that those cases which puzzled the ophthalmologists most were nearly always those in which there were complicating diseases of the eye or atypical reduction of the visual fields Most of these patients had, however, already at the time of the first examination by the eye-specialist had co-existing symptoms of the adenoma, usually disturbances of gonadal function, which would have helped the doctor to make an early diagnosis if the patients had been asked for them An eminent ophthalmologist (CAMLIN & DAVIDOFF 1955) pointed out that "perhaps even more important than the visual field is a very carefully taken history"

Many authors have emphasized that headache is a very common and important symptom of chromophobe pituitary adenoma (HENDERSON 1939, YOUNGHUSBAND ET AL 1952, BARRET 1953, SHELINE, BOLDREY & PHILLIPS 1964) NURNBERGER & KOREY (1953) pointed out that it is often frontal and fairly frequently unilateral and localised to the orbital region This localisation was common in the present series In these patients the adenoma had often spread asymmetrically to the side on which they had headache

In some cases the headache disappeared with appearance of the visual disturbances This coincidence has also been described by BAILEY (1932) and SCHNITKER ET AL (1938) This change in the type of symptom is thought to be due to the expanding adenoma having ruptured the diaphragma sellae with cessation of the tension

Many of the patients had had episodes of severe headache together with dizziness and vomiting, sometimes of migraine- or Meniere-like type At least one of the patients in this series appeared to have typical Meniere s disease, but the periodic attacks of headache in this patient were followed by headache of constant type, certainly due to the expanding adenoma Headache in associ

ation with menstruation was also noted, a finding reported also by NURNBERGER & KOREY (1953) In many of these cases the significance of the headache had surely been underestimated and the symptoms not been properly investigated

Epilepsy is a fairly uncommon symptom of chromophobe pituitary adenoma before treatment (BAKAY 1950 NURNBERGER & KOREY 1953, CLARKE KNIGHTON & BEBIN 1963, SHELINE, BOLDREY & PHILLIPS 1964) As in the present series it usually leads to neurological examination of the patient and thereby to the diagnosis of his condition

Occasionally the pituitary adenoma can assume considerable dimensions without producing any symptoms For example in the present series one of the patients had had moderate headache for a few months and roentgen examination for allergic rhinitis incidentally revealed the tumour At the time of the diagnosis the patient was 14 years old and the adenoma was probably the largest in the entire series

Polydipsia and polyuria are uncommon symptoms of chromophobe pituitary adenoma at the time of the diagnosis (YOUNGHUSBAND ET AL 1952 PRIBRAM & SWANN 1960 CLARKE, KNIGHTON & BEBIN 1963) These symptoms are much more common in craniopharyngioma indicating disturbed function of the hypothalamus (MULLER & WOHLFART 1950 WISE ET AL 1955 PRIBRAM & SWANN 1960)

It is generally agreed that symptoms of functional disturbances of the gonads in either sex are by far the commonest and earliest signs of incipient pituitary insufficiency (HENDERSON 1939, NURNBERGER & KOREY 1953, HEINBACH 1959 POPPEN 1963)

NURNBERGER & KOREY (1953) reported a correlation between chromophobe pituitary adenoma and irregular menstruation Such a relationship can of course not be demonstrated in retrospect but in some of the present cases the menstrual disorders were probably due to the tumour Occasional cases of Turner s syndrome have been described with pituitary adenoma (PETERS ET AL. 1954 WILLEMSE 1962 MILCU ET AL 1964 BASSO ET AL. 1965) A case of this type was also seen in the present investigation

An analysis of the individual cases in the present series suggested that the diagnosis could have been made earlier if amenorrhoea had been recognised as an early symptom of hypophyseal insufficiency in chromophobe pituitary adenoma The development of the symptoms also suggests that repeated radiologic examination of the sella turcica might be useful in the examination of patients with amenorrhoea of obscure origin and that a thorough inquiry should be made into the patient s personal history for symptoms of insufficiency of other target organs (thyroid and adrenal cortex)

The investigation of the anamnestic symptoms showed that it is important that the males complaining of tiredness and other diffuse symptoms are interviewed about their sexual activity Unlike females males rarely consult their doctor directly for disturbances in sexual

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CHAPTER III

TREATMENT OF TUMOUR

The methods of treatment of chromophobe adenoma have been successively improved during the 40-year period covered by the present investigation Until the beginning of the 1930s roentgen treatment was the only treatment available in Sweden The first operation in a patient belonging to the present series was done 1931 From 1933 on it has been possible to offer surgical treatment in all cases where operation was indicated

Before 1946 all patients to be operated upon were referred to the neurosurgical department Serafimerlasarettet, Stockholm From 1946 on all patients belonging to the present material were operated upon at the department of neurosurgery in Lund

In the first 25 years the patients received roentgen treatment either at Lasarettet, Lund or at their local hospital From 1946 on all but 8 patients received radiotherapy at the department of radiotherapy in Lund which serves a large catchment region

METHODS AND INDICATIONS FOR SURGICAL TREATMENT

The transfrontal approach was used in 109 cases The lateral lower part of the frontal lobe was exposed by the osteoplastic flap method After incision of the tumour capsule usually between the optic nerves, as much as possible of the intracapsular tissue was removed the proportion excised varying with the consistency, size and shape of the growth Readily accessible parts of the capsule were also extirpated It was never possible to remove the entire tumour

In 5 cases the operation was limited to the removal of biopsy specimens to confirm the diagnosis (Nos 62 68, 71 77 and 96) In these cases it was intended to treat the patients with a stereotaxic radiation technique

The transsphenoidal approach was used in 2 cases (Nos 117 and 119) The sphenoidal cavity was opened via the maxillar sinus and posterior ethmoidal cells on one side in accordance with the technique developed by HAMBERGER & NORLÉN (HAMBERGER ET AL. 1961)

The indication for operation was compression of the optic chiasma and nerves None of the patients in the present series were operated upon unless they had symptoms of such compression.

function or if they do, they initially pretend they have come to inquire about some other symptom instead This has also been pointed out by YOUNGHUSBAND ET AL (1952) The males could often date their loss of libido and potency fairly exactly They often reported simultaneous symptoms of androgenic insufficiency, *e g*, that they did not need to shave so often as before This information indicates the symptoms being caused by the growing adenoma

More or less pronounced symptoms such as cold intolerance, tiredness and weakness, sometimes with associated reduced activity and mental sluggishness were reported by one third of the present patients These symptoms may be an expression of hypopituitarism and mainly of secondary adrenocortical insufficiency (SCHNITKER ET AL 1938, NURNBERGER & KOREY 1953, KOEPFF & VIEILLARD 1954, WHITTAKER & WHITEHEAD 1954, JEFFERSON 1957)

It is well known that various types of intracranial expanding processes can cause headache, increasing loss of initiative, sluggishness, periods of disorientation and loss of consciousness leading to more or less profound coma In several of the cases belonging to the early period covered by the present investigation, symptoms of this type were described In a patient with radiologically demonstrated pituitary tumour and thus clinical picture, it must be realised that all the symptoms may be due to coexisting adrenocortical insufficiency, as pointed out by JEFFERSON (1957) and CAUGHEY (1958)

In the present investigation about 70 % of the patients consulted an opthalmologist first because of their visual disturbances, the remaining 30 % consulting an internist In one fifth of the cases the disease was diagnosed more than 2 years after their first consultation This delay was the same whether they first consulted an ophthalmologist or an internist It is remarkable that many of the patients were treated for such a long time with various tonics and other ineffective drugs though the true nature of their condition had not been recognized

The investigation thus showed that certain symptoms or groups of symptoms are of practical significance in the diagnosis of chromophobe pituitary adenoma visual disturbances, headache, symptoms suggesting endocrine insufficiency It is important to make a thorough inquiry into the patient's history and not to belittle such apparently trivial symptoms as headache and weakness Especially combinations of the above symptoms should direct the examiner's thoughts to the probability of chromophobe pituitary adenoma

Table 4 *One hundred and thirty one patients with chromophobe pituitary adenoma grouped according to type of treatment*

Type of treatment	Total	Operative deaths	Roentgen treatment with technique used before 1946	since 1946
		Number of patients		
A *Combined* (operation and roentgen treatment)				
1) Transfrontal approach	78	9		69
2) Transfrontal approach	15	1	14	
3) Transfrontal approach biopsy only	5			5
4) Transsphenoidal approach	2			2
B *Surgical only* (transfrontal approach)	7			
C *Radiation only*				
1) Patients with compression of the optic chiasma	19		14	5
2) Patients without compression of the optic chiasma	5		2	3

1) TRANSFRONTAL APPROACH AND RADIATION WITH UNIFORM MEDIUM VOLTAGE TECHNIQUE —This group consists of 78 patients in whom postoperative irradiation with the technique used since 1946 was intended There were however 9 deaths (Nos 37 40, 85 87, 125 126, 127 128 and 131) from postoperative complications Four of these patients had survived 3 to 13 months but their poor condition made roentgen treatment impossible

The group of 69 patients, who survived the operation may be regarded as fairly uniform from a therapeutical standpoint All the patients were operated upon with the transfrontal approach, and attempts were made to remove as much of the adenoma as possible Most of these operations were performed by one and the same surgeon All the patients received postoperative roentgen treatment by the technique used since 1946 at the department of radiotherapy in Lund

The time-dose relationship is demonstrated in a double logarithmic diagram (fig 3, *see next page*)[1] In the diagram 4 cases are specially marked They will be further discussed in Chapter VII

2) TRANSFRONTAL APPROACH AND RADIATION WITH OLD TECHNIQUE —This group consists of 15 patients in whom postoperative irradiation with old technique was intended One patient (No 21) died however from complication at the operation Fourteen patients received postoperative irradiation with the technique used before 1936 Some of these patients received single short series of roentgen treatment with tumour doses which were later calculated from available data as being less than 1,000 r (e g Nos 25, 29 and 31) Other patients received treatment with multiple short series given during a relatively long period, in 2 cases (Nos 14 and 39) spread over 7 and 4 ½ years The size of

[1] I wish to thank Dr T Andersson, department of radiotherapy Lasarettet Lund for valuable help with calculating the tumour doses given

METHODS AND INDICATIONS FOR ROENTGEN TREATMENT

Radiation technique Medium voltage roentgen treatment was given throughout *Technical data* 170 kV, 2 mA, FSD 50 or 60 cm Filter 0 5 Cu + Al, HVL 0 9 mm Cu

Up to 1946 the technique used was not uniform The radiation was given via one field in each temporal region, sometimes also a field in the frontal or parietal region As a rule, the treatment was administered as multiple courses given at long intervals with small tumour doses in each course

From 1946 treatment was uniform a cross radiation from 2 fields in each temporal region At roentgen examination the site of the sella turcica and that of the centre of the tumour were marked with indicators in each temporal region The skin fields were then placed symmetrically, *i e* cranially respectively caudally, to this point The field size varied from 4 by 4 cm to 6 by 6 cm according to the size of the tumour At each treatment the central ray was adjusted with a backpointer from the middle of the upper field on one side to the middle of the lower field on the other side or *vice versa* One skin field was treated per day with a skin dose of 300—400 r The skin dose was checked by measurement with an ionization chamber The tumour dose, as calculated with the aid of depth dose tables, was 30—35 % of the skin dose delivered to each field

From 1946 treatment was given in a single coarse or two coarses, with an interval of 4—5 weeks in between

The total skin dose delivered to each field varied from 2,800-4,000 r according to the fractionation time

Stereotaxic roentgen treatment according to a special technique was given in 2 cases With the aid of a stereotaxic instrument (Leksell 1955) the beam was directed through the calculated centre of the adenoma, and treatment was given via 52 fields distributed over the entire scalp Field size 3 × 3 cm, and the calculated skin dose 300—600 r per field

Indications for roentgen treatment —After surgical treatment of pituitary adenoma became available the indications for roentgen treatment remained principally unchanged The patients received postoperative radiotherapy, and when operation was not indicated, because of the absence of compression of the optic chiasma, the patients were primarily treated with radiation only

CLASSIFICATION OF CASES ACCORDING TO TYPE OF TREATMENT

In the evaluation of the results of the various types of treatment the patients were divided into three groups (Table 4) The individual treatment of the patients is accounted for in Table 16, Appendix

A COMBINED TREATMENT (OPERATION AND ROENTGEN TREATMENT)

Ninety patients were treated with operation followed by irradiation Since the roentgen treatment was not uniform throughout the series, and since attempts were not made to remove as much of the tumour tissue as possible at operation in 5 cases, and 2 cases were operated upon by the transsphenoidal approach, this group was divided into 4 subgroups

(Nos 65 and 73) stereotaxic roentgen treatment was intended but had not been given

E ROENTGEN TREATMENT ONLY

This group which consisted of 24 patients, was divided into two groups with and without compression of the optic chiasma and nerves

I) PATIENTS WITH COMPRESSION OF THE OPTIC CHIASMA —Nineteen of these 24 patients had received roentgen treatment only, though their records suggested that they had compression of the optic chiasma and nerves In 12 (Nos 1—10, 13 and 15) of these 24 patients however, the diagnosis had been made before the introduction of surgical treatment of pituitary adenoma in Sweden i e before the beginning of the 1930 s One patient (No 20) in whom the diagnosis was made in 1939 had refused operation and had therefore been given roentgen treatment In 6 cases the risk of operation had been considered too great In 5 of them (Nos 22 41, 55 104 and 109) roentgen examination had shown very large adenomas and the patients were in a bad condition In 1 case (No 82) operation had been contraindicated by thrombocytopenia

II PATIENTS WITHOUT COMPRESSION OF THE OPTIC CHIASMA —Five patients (Nos 19 28 99 102 and 115) had not been operated upon because they had no ophthalmoneurological signs of compression of the optic chiasma In one (No 99) of them the adenoma had however extended 14 mm over the entrance of the sella in the roentgenogram Two of these 5 patients received roentgen treatment with the technique used before 1946 (Nos 19 and 28) and the other 3 with the later used technique

COMMENTS

The indication for operation in the present series differed from those used in other series on record (DAVIDOFF & FEIRING 1948 KERR 1948, HORRAX 1958, CORREA & LAMPE 1962 and POPPEN 1963) In these series operation was considered indicated only when the patients had severe or rapidly progressing ophthalmoneurological changes and patients in whom the diagnosis of pituitary tumour was uncertain Patients with less pronounced visual disturbances were given radiation only, and operation was resorted to only if the visual disturbances progressed despite roentgen treatment In the present series however, operations were performed even on patients with relatively small tumours and typical ophthalmoneurological changes suggesting *suprasellar expansion of* the adenoma with compression of the optic nerves and chiasma The indications accepted were largely those recommended by CUSHING (HENDERSON 1939) and OLIVECRONA (BAKAY 1950)

CUSHING first used the transsphenoidal technique but soon preferred the transfrontal approach (HENDERSON 1939) The somewhat higher operative mortality with the last mentioned technique is according to Cushing outweighed by the advantage of a better view of the field of operation and by immediate recognition of the extension of the tumour It also provides a better possibility of

the total tumour dose in these cases could not be calculated from available data

3) TRANSFRONTAL APPROACH (BIOPSY ONLY) AND RADIATION —In 5 cases where stereotaxic roentgen treatment had been intended, the operation was limited to removal of a biopsy specimen (see page 28) *However, the special roentgen* treatment intended was used in only 2 (Nos 62 and 96) of the cases, while the others were treated with the technique used since 1946

4) TRANSSPHENOIDAL APPROACH AND RADIATION —Operation with the transsphenoidal approach was done *in 2 cases* (Nos 117 and 119) In both cases *roentgen* examination had suggested *adenoma mainly* of intrasellar type Both patients received postoperative roentgen treatment with the technique used since 1946

II SURIGICAL TREATMENT ONLY

This group consisted of 7 patients who had, for various reasons, not received *roentgen treatment* Two (Nos 16 and 17) of the patients belonging to the early part of the series did not present themselves *for intended postoperative roentgen treatment* For some unknown reason 3 patients (Nos 36, 47 and 90) had *not received such treatment In 2 cases*

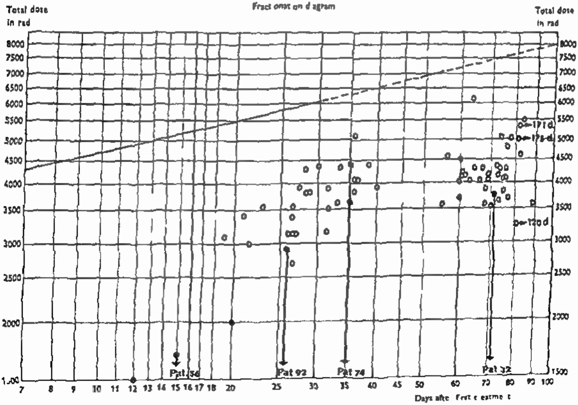

Figure 3 *Roentgen treatment (tumour doses) given to 69 patients with chromophobe pituitary adenoma treated with transfrontal operation and uniform medium voltage roentgen technique Three patients are marked with an arrow and the number of days for treatment (more than 100 days) Unbroken line indicates healing of skin cancer according to* STRANDQUIST *(1944) dotted line denotes the extrapolarisation to a duration of 100 days of treatment*

= patients without sings of recurrence during survival or until end of 1965
= patients treated for recurrence, no further sings of recurrence until end of 1965
= patients dead after uncontrolled growth of tumour For further comments see Chapter VII

CHAPTER IV

VISUAL DISTURBANCES

The diagnostic value of careful ophthalmoneurological examination of patients with suspected chromophobe pituitary adenoma has been stressed by various authors As mentioned earlier, the occurrence of visual disturbances plays a decisive role in the choice of treatment Ophthalmoneurological examination is also important after treatment to assess the effect of therapy and it is necessary at the later follow up in order to detect any recurrence of the adenoma

Before 1954 the ophthalmoneurological examinations in the present series had not been performed according to uniform principles The results of the visual field examinations before 1954 are not strictly comparable to those made after this time Besides this the notes on visual field examinations in the beginning of the series were sometimes incomplete

From 1954 on all the patients were examined with the aid of quantitative perimetry with white objects according to a routine method described by ENOKSSON (1965) The examinations were carried out mainly with Goldmann s projection perimeter All examinations after 1954 were performed by two examiners (Enoksson and Bynke)

Hereinafter visual status before and after treatment is to be understood as the status of the patient immediately before treatment, and after treatment had achieved its full effect, or after retreatment of a recurrence The ophthalmoneurological status was controlled at re examination in 78 of the 80 living patients

The results of the examination of visual field and visual acuity before and after treatment in the individual cases are presented in T ble 16 in the appendix where the changes are given by name of a particular code accounted for in Tables 5 and 7 in this chapter

Visual disturbances before and after treatment are accounted for and discussed in this chapter In the small treatment groups only the changes of the visual caqacity as a function of the visual fields and visual acuity are described. In the 69 patients treated with transfrontal operation and uniform roentgen technique (treatment group A 1) the changes in the visual status will however be discussed in greater detail

dealing with complications (such as bleeding) during the operation

In recent years the transsphenoidal approach has begun to be used more often (HIRSCH 1959 and GUIOT & THIBAUT 1959) recommend this method in cases of *chromophobe pituitary* adenoma regardless of the size and extension of the latter According to several other authors (HAMBERGER ET AL 1959, 1961 a, 1961 b, POPPEN 1963, WHITE 1964, SHELINE, BOLDREY & PHILLIPPS 1964, JACKSON 1965), however, this surgical technique should only be used in the treatment of cases with mainly intrasellar tumours and it is only justified if roentgen examination has verified the diagnosis (pneumoencephalography and angiography of the internal carotid) and shown that the tumour is mainly intrasellar

Opinions thus differ on the choice of operation The majority of neurosurgeons, however, use the transfrontal approach as a routine method in the surgical treatment of chromophobe pituitary adenoma

As in Olivecrona's series (BAKAY 1950) combined treatment, operation and roentgen therapy, was used in the present series on the basis of HENDERSON's (1939) experience in Cushing's series of patients with chromophobe pituitary adenoma

The roentgen technique used in the present series before 1946 was largely the same as that used by HENDERSON (1939), BAKAY (1950), YOUNGHUSBAND ET AL (1952) and NURNBERGER & KOREY (1953) BACHMAN & HARRIS (1949) compared the effect of the previously used multiple-course technique, delivering a fairly small dose in each treatment course, with that of a more intense single-course radiation They found a tumour dose of about 3,000—4,000 r given over 30—45 days to be followed less frequently by recurrences Similar experience has been reported by several authors, who used either conventional medium voltage technique or different forms of high voltage technique with a total tumour dose of about 4,000 r (HORRAX 1958, HEINBACH 1959, DECKER & LAUTER 1960, RAY & PATTERSON 1962, POPPEN 1963, SHELINE, BOLDREY & PHILLIPS 1964) The same dose given by conventional medium voltage technique, had been aimed at in the present series

The results of treatment with reference *inter alia* to the operative mortality, the incidence of recurrences and the survival time are accounted for in Chapter VII

treatment Her visual fields had however, become rapidly reduced during 2 pregnancies with an interval of 4 years The visual status became normal within 3 weeks respectively 5 months after each parturition Even 5 months after the last parturition, however the encephalogram showed suprasellar tumour extending 17 mm above the sellar opening In view of this serious threat to vision the patient was operated upon and received postoperative roentgen treatment When last seen 5 years after treatment her visual status was still normal (see also p

Incomplete bitemporal hemianopia — Twenty nine patients had incomplete bitemporal hemianopia before treatment In 9 of them the visual fields became normal In 18 considerable improvement was noted but small bitemporal field defects persisted In 1 patient (No 46) the defects increased after treatment but then remained unchanged and did not progress further during the following 10 years One patient (No 89) developed central scotoma due to a retinochoroiditis not related to the basic disease or to treatment of it

Complete bitemporal hemianopia Thirteen patients had complete bitemporal hemianopia before treatment After treatment the visual fields improved in 6 but remained largely unchanged in 3 A further reduction of the visual fields was observed in 4 patients after treatment in 1 (No 69) nasal defects and in 2 (Nos 32 and 113) paracentral scotoma supervened and in 1 (No 63) incongruent central defects because of senile degeneration of the macula 4 years after treatment supervened

One eye unaffected the other amaurotic or only perception of light —In 2 (Nos 66 and 118) of these 5 patients vision on one side had decreased to less than 0 1 a short time before treatment In these cases a considerable and permanent improvement or complete normalisation of the visual field and acuity occurred after treatment One patient (No 48) had since birth been blind on one eye because of microphthalmia At 58 years the visual acuity of the normal eye decreased while the visual field was still normal She had an asymmetric adenoma under the optic nerve on the side where she was blind In 1 case (No 45) treatment was followed by slight loss of the temporal field of the only serviceable eye In 1 patient (No 67) treatment was followed by altitudinal lower hemianopia on one eye while the other was still amaurotic after treatment

Bitemporal hemianopia and limitation of the nasal field —Bilateral considerable visual field defects were noted in 10 patients before treatment In 3 (Nos 84 93 and 108) treatment gave good improvement and in 5 the visual status remained largely unchanged In 1 (No 120) of these 5 patients only the left nasal half of the visual field was preserved Two patients (Nos 81 and 100) had only small nasal visual fields left, and after treatment vision was decreased to perception of light

Atypical visual field defects —In 8 patients atypical defects were noted before treatment In 5 of them (Nos 32 55 56 106 and 123) there were more or

Table 5 Sixty nine patients distributed according to severity of visual field defects before and after combined treatment of chromophobe pituitary adenoma with transfrontal operation and roentgen technique used since 1946
Visual field defects

- ■ Normal visual fields
- 1 Incomplete bitemporal hemianopia
- 2 Complete bitemporal hemianopia
- 3 One eye unaffected the other amaurotic or only light perception
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- 5 Homonymous hemianopia and/or paracentral scotoma
- 6 Amaurosis, light perception or only small nasal remnants

Before treatment Visual field defects		After treatment ■	1	2	3	4	5	6
	Number of patients	11	32	4	2	9	6	5
■	1	1						
1	29	9	18			1	1	
2	13		6	3		1	3	
3	5	1	1		1	1	1	
4	10		2	1		5		[illegible]
5	8		5		1	1	1	
6	3							3

A COMBINED TREATMENT (OPERATION AND RADIATION)

1) TRANSFRONTAL OPERATION AND RADIATION WITH UNIFORM MEDIUM VOLTAGE TECHNIQUE — This group consisted of 78 patients in whom postoperative radiation with uniform medium voltage technique was intended Nine of these patients died, however, from complications at or after operation Of these patients 6 had severe reduction of the visual fields Three of them (Nos 40, 87 and 125) thus had bitemporal hemianopia and nasal field defects Two patients (Nos 85 and 126) had complete homonymous hemianopia and 1 patient (No 37) had temporal hemianopia and paracentral scotoma on the one serviceable eye Only 3 (Nos 127, 128 and 131) of these 9 patients thus had moderate reduction of the visual field and of visual acuity

In the surviving 69 patients, uniformly treated with transfrontal operation and radiation, the effect of treatment on the visual fields and visual acuity will be reported The effect of reduction of visual fields and acuity on visual capacity will also be discussed

VISUAL FIELDS

Table 5 gives the distribution of the patients regarding the most important defects of the visual fields before and after treatment The visual field defects are accounted for largely according to their disabling effect

Normal visual fields — One patient (No 129) had normal visual fields just before

treatment Her visual fields had however, become rapidly reduced during 2 pregnancies with an interval of 4 years The visual status became normal within 3 weeks respectively 5 months after each parturition Even 5 months after the last parturition however the encephalogram showed suprasellar tumour extending 17 mm above the sellar opening In view of this serious threat to vision the patient was operated upon and received postoperative roentgen treatment When last seen 5 years after treatment her visual status was still normal (see also p

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4	10		2	1		5		2
5	8		5		1	1	1	
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Before treatment Visual field defects		After treatment 0	1	2	3	4	5	6
	Number of patients	11	32	4	2	9	[illegible]	5
0	1	1						
1	29	9	18			1	1	
2	13		6	3		1	3	
3	5	1	1		1	1	1	
4	10		2	1		5		2
5	8		5		1	1	1	
6	3							3

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Table 7 *Sixty nine patients distributed according to impairment of visual acuity before and after combined treatment of chromophobe pituitary adenoma with transfrontal operation and roentgen technique used since 1946*

Visual acuity		Visual incapacity according to Kungl Forsakringsradet 1927 (Nordin 1955) per cent
0	1.0/1.0	0
I	1.0–0.7/0.9–0.7	0
II	1.0–0.7/0.6–0.0–0.4/0.3	5–20
III	0.6/0.0–0.3/0.2	25–32
IV	0.4/0.0–0.2/0.0	40–50
V	0.2/0.0–0.0/0.0	65–100

Before treatment: Visual acuity		After treatment: 0	I	II	III	IV	V
	Number of patients	27	5	24	1	4	8
0	7	7					
I	10	8	1	1			
II	33	11	3	15		3	1
III	7		1	6			
IV	7	1		2		1	3
V	5				1		4

the distribution of the patients to the left and right of the diagonal

VISUAL ACUITY

Reduced visual capacity can be judged easiest by assessment of visual acuity A patient with well preserved or normal acuity on one eye and markedly reduced visual acuity on the other can however, as a rule adjust himself to the impairment, which therefore need not reduce his working capacity The purpose of the present investigation was among other things, to ascertain the effect of the treatment on working capacity To illustrate the degree of reduced visual acuity before and after treatment, the cases were classified in accordance with the table of *Kungl Forsäkringsrådet* 1927 (Table 6) for assessment of degrees of disability from eye accidents (Nordin 1955) In Table 7 the present cases were grouped according to impairment of visual capacity calculated as the percentage of normal visual capacity The tables give the effect of treatment on visual acuity

Of the 69 patients discussed here, the visual acuity was *normal* on both eyes in 7 before as well as after treatment. In 10 it was *slightly reduced*, but never less than 0.7 on one or both eyes before treatment In 8 of these 10 patients the visual acuity on both eyes became normal after treatment In 1 patient (No 59) the status was unchanged and in 1 (No 46) it became worse

Table 6 *Table for calculation of disability, expressed in per cent of normal visual acuity of patients with impairment of vision because of eye injuries (Kurgl Försäkringsrådet 1927* Nordin 1955)

	Visual acuity of the one eye							
	1 0—0 7	0 6	0 5	0 4	0 3	0 2	0 1	0 0
Visual acuity of the other eye	Visual incapacity per cent							
1 0—0 7	[illegible]	1	3	5	10	12	15	20
0 6		3	5	10	12	15	20	25
0 5			10	12	15	20	25	32
0 4				15	20	25	32	40
0 3					25	32	40	50
0 2						40	50	65
0 1							65	80
0 0								100

Ex If visual acuity = 0 7 on one side and 0 0 on the other the calculated disability will be 20 %
If the visual acuity on both sides = 0 1, the degree of disability will be 65 %

less pronounced homonymous defects before treatment, in 2 of them (Nos 32 and 106) there was also unilateral paracentral scotoma In 3 (Nos 59, 78 and 95) scotoma of one or both fields was the only change

A considerable improvement of the visual fields was observed in 5 of these 8 patients, who had only defects of the temporal fields after treatment In 1 (No 32) of these 5 patients the tumour recurred with progressive visual disturbances and the patient died 4 years later from the tumour In 2 patients operation was followed by amaurosis on one eye, while the other field was normal (No 56) or had a temporal defect (No 123) In patient No 56 a slight defect of the visual field was noted on the better eye in association with a recurrence 11 years after treatment After re-operation and further radiation, vision on that eye became normal and was still unchanged at examination 4 years later One patient (No 106) after treatment had a large temporal defect in the left field and a nasal paracentral scotoma in the right

Amaurosis or only light perception — Three patients (Nos 42, 60 and 74) had very low visual acuity before treatment, so that it was not possible to examine the visual fields *No appreciable improvement* occurred after treatment Two of the patients had large adenomas

As to the visual fields in the 69 patients treated by operation and radiation, improvement was noted in 27 (Table 5) In the table these patients are entered to the left of the diagonal In 32 patients the visual fields were judged as unchanged after treatment These patients are entered along the diagonal in the table In 10 the reduction of the visual fields had increased after treatment, and in the table these cases are entered to the right of the diagonal The degree of improvement or deterioration in the various groups, classified according to the type of visual field impairment before treatment, thus is illustrated by

Table 7 *Sixty-nine patients distributed according to impairment of visual acuity before and after combined treatment of chromophobe pituitary adenoma with transf ortal operation and roentgen technique used since 1946*

Visual acuity		Visual incapacity according to Kungl Forsakringsrådet 1927 (NORDIN 1955) per cent
0	1 0/1 0	0
I	1 0—0 7/0 9—0 7	0
II	1 0—0 7/0 6—0 0—0.4/0 3	1—20
III	0 6/0 0—0 3/0 2	25—32
IV	0 4/0 0—0 2/0 0	40—50
V	0 2/0 0—0 0/0 0	65—100

Before treatment: Visual acuity		After treatment: 0	I	II	III	IV	V
	Number of patients	27	5	24	1	4	8
0	7	7					
I	10	8	1	1			
II	33	11	3	15		3	1
III	7		1	6			
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V	5				1		4

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Visual acuity of the other eye	Visual acuity of the one eye: 1·0–0·7	0·6	0·5	0·4	0·3	0·2	0·1	0·0
	Visual incapacity, per cent							
1·0–0·7	0	1	3	5	10	12	15	20
0·6		3	5	10	12	15	20	25
0·5			10	12	15	20	25	32
0·4				15	20	25	32	40
0·3					25	32	40	50
0·2						40	50	65
0·1							65	80
0·0								100

Ex If visual acuity is 0·7 on one side and 0·0 on the other the calculated disability will be 20 %. If the visual acuity on both sides is 0·1, the degree of disability will be 65 %

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degree of improvement or deterioration of visual acuity is apparent from Table 7

VISUAL CAPACITY

In a series of patients with chromophobe pituitary adenoma the visual capacity can of course, not be judged only by visual acuity Consideration must also be given to the type and the extent of limitation of the visual fields The patients' occupation before onset of the disease must also be taken into account in assessing the degree of visual disability

An attempt was made to assess the incidence of disabling reduction of the visual capacity in the present series The visual capacity was analysed regarding the ability of the individual patients to carry on with their usual occupation and to what extent the reduction of visual capacity interfered with their daily life Pensioners were regarded as disabled if they could no longer take care of themselves because of reduction of visual capacity

This investigation showed that disabling reduction of visual capacity occurred in 18 of the aforementioned 69 patients before and in 12 after treatment that the degree of disability cannot be judged simply from the reduction of visual acuity and that the patient's ability to adapt himself must also be considered This ability may be exemplified by a few illustrative cases

In one (No 120) of the above mentioned patients vision was limited to the nasal field of the left eye before as well as after treatment She was obliged to give up her job as a clerk and to take household work, though her visual acuity on that side was 0 9—1 0, which corresponds to only 20 % disability according to Table 6 (group II in Table 7) A similar extensive loss of visual fields but fully serviceable visual acuity had no effect on the working capacity of a farmer (No 93) or 2 pensioners (Nos 105 and 130) Two patients, an unskilled labourer (No 45) and a parson (No 56) had before treatment a visual acuity of 0 6 but only slightly reduced visual field on the one and only serviceable eye Their working capacity was not severely impaired by this visual impairment In 2 patients (Nos 63 and 89) a business executive and a small farmer, visual acuity as well as the visual fields were markedly reduced after treatment Nevertheless, both of them could carry on fairly well with their occupation

All of the above mentioned patients with disabling reduction of visual capacity, except patient No 120 had a reduction of visual acity corresponding to at least 25—32 % visual disability according to Table 6 (groups III—V in Table 7) This table is used by Swedish insurance companies in the evaluation of the disabling effect of reduced visual acuity due to accidents It cannot of course, be applied forthwith in evaluation of the degree of disability of patients with chromophobe pituitary adenoma, because of the co-existing reduction of the visual fields In most cases this reduction caused further disability corresponding to 20—25 % over and above that due to reduction of visual acuity

Of the 18 patients with visual in

Moderately reduced visual acuity on one or both eyes, corresponding to 1—20 % disability according to Table 6, was noted in 33 cases before treatment In 14 of them visual acuity after treatment was normal (11 cases) or markedly improved (3 cases) In 15 cases visual acuity remained largely unchanged after treatment A substantial deterioration was noted in 4 cases, with complete loss of vision on one eye in 2 (Nos 67 and 69), and in 2 (Nos 63 and 89) it fell to 3—4/60, while in all 4 visual acuity was 0 4—0 1 on the other eye In the 2 last mentioned patients the impairment of vision was, however, due to senile degeneration of the macula respectively scars after retinochoroiditis

Of the above mentioned 33 patients there was a marked asymmetric impairment of vision in 19 The visual acuity on the one eye was 1 0—0 7, *i e*, fully serviceable acuity, while it was at least 0 7 lower on the other eye In 4 patients (Nos 33, 91, 98 and 118) with normal visual acuity on one eye, severe impairment of vision had been noticed on the other eye for 1—6 months before treatment In all of these patients vision improved markedly or completely after treatment A rapid improvement after the operation also occurred in some other patients, most strikingly in patient No 103 whose visual acuity was 0 4/0 4 before operation but normal 5 days after the operation

Fairly *marked reduction* of the visual acuity, corresponding to 25—32 % disability (Table 6), was observed in 7 patients before treatment Improvement was marked in 1 (No 32) and moderate in the remaining 6 Patient No 32 had a large adenoma The effect of treatment was only temporary and he died 4 years later from uncontrolled growth of tumour

Pronouncedly *reduced* visual acuity corresponding to at least 40 % disability, occurred in 12 cases before treatment, 5 of them having at most 0 2 on the only serviceable eye In 3 of these patients the reduction of the visual acuity had occurred shortly before treatment it became normal in 1 (No 97) and improved considerably in 2 (Nos 52 and 83) Some improvement was noted in 1 patient (No 35), but the visual acuity was also afterwards reduced on one side because of anisometropia In 8 patients (Nos 42, 50, 60, 74, 76, 81, 95 and 100) visual acuity was further reduced so that also afterwards these patients were largely dependent on the help of others In 1 (No 76) of them the impairment of vision was due to sequelae after haemorrhage in the macula region, which had occurred before the diagnosis

Of the group of 69 patients all treated with transfrontal operation and uniform roentgen technique, 7 had normal visual acuity before as well as after treatment More or less considerable improvement was noted in 33 patients, including 11 in whom visual acuity was markedly reduced before treatment These 33 patients are placed to the left of the diagonal in Table 7 In 21 patients the reduction of the visual acuity after treatment was unchanged and in 8 it was more pronounced It should be observed that in 3 of these 8 cases the deterioration was due to incidental eye diseases The

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Of the 18 patients with visual in-

capacity before treatment, 8 had only moderate impairment of visual capacity for a short time before treatment (Nos 32, 52, 66, 79, 83, 97, 106 and 123) After treatment visual capacity improved and all 8 returned to their usual occupation In 10 of them (Nos 35, 42, 50, 60, 74, 76, 81, 95, 100 and 120) the visual incapacity persisted also after treatment, in 4 (Nos 50, 60, 81 and 100) it was so severe that they could afterwards not take care of themselves Two patients (Nos 67 and 69), in whom the visual fields were slightly reduced before treatment, experienced marked deterioration after treatment of visual acuity and fields of the only serviceable eye so that they could not manage their daily life by themselves

2) TRANSFRONTAL OPERATION AND RADIATION WITH THE OLD TECHNIQUE — This group consisted of 15 patients in whom postoperative irradiation with the old technique was intended One of them (No 21), however, died at operation He had severe visual field defects with only small nasal remnants In 9 of the other patients, there was also disabling impairment of vision before treatment, while in 5 (Nos 24, 29, 31, 38 and 39) the reduction of the visual fields was less severe

In 3 patients (Nos 11, 12 and 27), who had disabling impairment of vision, operation produced no improvement of vision In 11 patients vision improved or ceased to progress after treatment, so that for at least 4 years they were not disabled by impaired vision In 6 of them the ophthalmoneurological changes recurred after 4—25 years Re-operation and/or roentgen treatment produced only a temporary effect in 3 (Nos 18, 30 and 31) of them, while in 2 (Nos 14 and 29) the supervening changes regressed completely

3) TRANSFRONTAL OPERATION (BIOPSY ONLY) AND RADIATION — In 5 of the patients in this group surgery was confined to a minor operation to decompress the optic nerve (see Chapter III) In 2 patients (Nos 68 and 77) treatment was followed by a marked improvement In patient No 77 the visual status became normal This patient was re-examined 7 years after treatment He complained of several years' obstinate headache, but he had no ophthalmoneurological signs of suprasellar extension He died 1 year later from a large recurrence of the adenoma, which had by then extended forwardly between the optic nerves without compressing them In 2 patients (Nos 62 and 96) with moderately reduced vision no improvement was noted The visual status was still unchanged at the time of the re-examination 12 respectively 8 years later In 1 patient (No 71) the visual field was markedly reduced already before treatment Despite good improvement of visual acuity of the one eye the patient could not return to his previous occupation, watch-maker, but was afterwards regarded as strongly disabled

4) TRANSPHENOIDAL OPERATION AND RADIATION —In the 2 patients in this group the visual field and visual acuity were only moderately reduced before treatment In one (No 119) of them

vision improved slightly, but in the other (No 117) it became normal after the operation This patient was, however, afterwards found to have a large asymmetric tumour one year later giving homonymous field defects

B SURGICAL TREATMENT ONLY

All 7 patients in this group had pronounced visual field defects before treatment Good improvement of the visual status was noted in all except 1 (No 17) who was also later disabled by his visual impairment This patient and another 3 (Nos 36 47 and 65) however, had a recurrence of the ophthalmoneurological changes as soon as 1—3 years after the operation Re operation was not followed by any appreciable visual improvement The improvement persisted in 3 (Nos 16, 73 and 90) of the patients during follow up (11—30 years) Patient No 73 had normal visual status on the only serviceable eye Thirteen years after operation he had a large recurrence of an asymmetric tumour which was not detected for a long time because it affected only the optic nerve of the amaurotic eye

C ROENTGEN TREATMENT ONLY

This group consisted of 24 patients who for reasons given previously received roentgen treatment only Of these 24 patients 19 had more or less pronounced ophthalmoneurological changes suggesting compression of the optic chiasma and nerves before treat ment while 5 patients had no such symptoms The entire group would lend itself well to an investigation of the effect of roentgen treatment only But the group included a large number of patients who had advanced longstanding ophthalmoneurological changes already before treatment In several of these cases, the general condition of the patients was so poor as to contraindicate operation and only a palliative effect could be expected from roentgen treat ment

1) PATIENTS WITH COMPRESSION OF THE OPTIC CHIASMA —This group consisted of 19 patients Fourteen were treated before 1940 with the older roentgen technique and 5 in 1950—1957 with the later technique Already before treatment as many as 11 of the patients in this group had visual field defects with complete bitemporal hemianopia as well as nasal defects, and 3 (Nos 6, 22 and 55) had homonymous defects and scotoma In 7 of them visual acuity was also markedly reduced, at most 0 2 on the better eye In all 19 patients in this group more or less good improvement of vision was observed after roentgen treatment In 10 of them, mostly with advanced visual disturbances before treatment, only a brief effect of treatment by the old roentgen technique was obtained, and all the patients died from the tumour within 1—5 years In 8 patients (Nos 1 2 4, 8 10 13 15 and 20), followed up for 6—36 years after treatment the old roentgen technique had produced good and permanent improvement or stabilisation of vision at a level not interfering with the patient s working capacity This was also the case in 1 patient (No 82) who however, died 1 year later from an incidental disease.

2) PATIENTS WITHOUT COMPRESSION OF THE OPTIC CHIASMA — In 4 of the 5 patients in this group there were no signs of optic nerve compression. In 1 (No 28) there was pronounced visual impairment secondary to severe arterial hypertension. The encephalogram showed no suprasellar extension of the tumour. Two patients (Nos 19 and 28) were treated with the older technique. Two respectively 4 years later, typical visual disturbances supervened and both patients were operated upon. The visual status improved in patient No 19, while in the other patient marked impairment of vision persisted. Three (Nos 99, 102 and 115) of the 5 patients were treated with the later roentgen technique. In these vision was normal 7—10 years after treatment and the adenoma showed no signs of further growth.

DISCUSSION

The various types of visual field defects and the degree of reduced visual acuity were roughly the same as in other large series (HENDERSON 1939, DAVIDOFF & FEIRING 1948, NURNBERGER & KOREY 1953, TONNIS, OBERDISSE & WEBER 1954, WISE ET AL 1955, HEIMBACH 1959, NOVER 1962).

The difficulties encountered in the ophthalmoneurological diagnosis of chromophobe pituitary adenoma have been discussed in Chapter II. But the observations made in the present series justify discussion of these difficulties also in this chapter. The delay they caused in the diagnosis, probably had a very unfavourable effect on the visual disturbances after treatment. The diagnostic difficulties were encountered, above all, in patients with unilateral impairment of vision or atypical visual field defects and in patients with incidental eye disease. LITTLE, CHAMBERS & WALSH (1965) found that a delay in diagnosis in these cases "is the rule and not the exception." It should, however, be stressed that more or less atypical visual field defects occur in about 10 % of all cases of chromophobe pituitary adenoma, so that the possibility of a pituitary tumour must be considered in all patients with such defects. In patients with incidental eye disease in the present series, such disease had caused impairment of vision for several years, but all these patients had sought medical advice because of further deterioration of vision. It should be stressed once more that most of the patients with atypical field defects had also other symptoms of pituitary tumour, particularly headache and symptoms of gonadal insufficiency. If the doctor had inquired about these symptoms, the diagnosis might have been made earlier.

It has often been claimed that the risks of operation are greater in patients with advanced ophthalmoneurological disturbances (HENDERSON 1939, BAKAY 1950, TONNIS, OBERDISSE & WEBER 1954, HEIMBACH 1959). This is natural since advanced chiasmal compression with considerable reduction of vision in pituitary tumour also implies substantial suprasellar extension. HEIMBACH (1959) thought that surgical treatment in patients with large adenomas and advanced visual disturbances is hazardous and therefore contraindicated.

Severe reduction of vision because of

a large adenoma in the present series was considered an urgent indication for surgical decompression of the optic nerves and chiasma. Experience gained in the present series showed that transfrontal operation and roentgen treatment of patients with large adenomas can, in the majority of cases arrest the progress of the ophthalmoneurological changes and in some cases even produce considerable improvement. It might be stated already here that the increased risk of operation in such cases is well justified by the relief such treatment can offer. These questions will be discussed further in Chapter VII.

In the present series operation had the best effect on the vision in patients with incomplete bitemporal hemianopia. If the patient had lost more than half of the visual field the chances of recovery however were poor, especially in patients with longstanding visual impairment. These observations apply also to patients treated because of recurrences of the *tumour*.

In previous investigations the effect of treatment on visual capacity has usually been given as the number of cases with improved, unimproved and worsened visual capacity (HENDERSON 1939, BAKAY 1950, TONNIS, OBERDISSE & WEBER 1952, MOGENSEN 1957, HEIMBACH 1959). A more detailed investigation was reported by NOVER (1962). He described the distribution of different combinations of visual field defects before and after surgical treatment of 100 patients with different types of pituitary adenoma. The degree of reduced visual acuity of each eye was however given separately (200 eyes). NOVER also grouped his patients according to improved, unimproved and worsened visual status. Description of the results of treatment in this way is of limited value because it says nothing about the total visual status or the degree of improvement after treatment.

HENDERSON (1939), BAKAY (1950), NURNBERGER & KOREY (1953) and HEIMBACH (1959) are probably the only authors, who related the results of treatment to working capacity. In 64 to 75 % of the patients in their series vision was sufficient to allow them to work. Of the present series, 84 % of the patients treated with transfrontal operation and radiation had sufficient visual capacity to allow them to continue with their occupation or if pensioners to allow them to be independent.

The American Medical Association Committee on Medical Rating of Physical Impairment (1955) presented a method for evaluating the reduction of the visual fields and acuity after accidents or disease. The impairment of vision was given *in per cent of* normal visual capacity. COLBY ET AL. (1964) used this method in the evaluation of the results of treatment in a series of patients with pituitary adenoma treated with irradiation.

The American method for evaluating visual disability is based *on the use of* Snellen tables for calculation of visual acuity. In the present material visual acuity was classified according to Monoyer—Granstrom's *decimal tables*. The values given for visual acuity in the present *series can not* be converted exactly into the units used in the Ameri

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CHAPTER V
RADIOLOGIC CHANGES

Radiologic examination of the sella turcica is important in the diagnosis of pituitary adenoma as is pneumo-encephalography which is also useful in the estimation of the extent of any extrasellar growth, knowledge of which is necessary in the planning of treatment

It was decided to extend the re examination of the present material to include a re study of the available roentgenograms on which the diagnosis had been based and of those taken during follow up This re study was performed in cooperation with Dr S Cronquist Neuroradiological section, department of radiology Lasarettet Lund The results of this re study have been previously published by CRONQUIST & FURST 1964

The size of the sella turcica was judged from measurements made in the way described previously The suprasellar portion of the adenoma if any was measured in the encephalogram Measurements were made from the upper pole of the tumour to a base line drawn from the nasion through a point where the sphenoid plane meets the anterior wall of the sella

SKELETAL CHANGES OF THE SELLA TURCICA

Roentgenograms taken *before treatment* showed *according to the roentgenologists* reports in the records changes of the sella turcica in all of the 131 patients except 2 (Nos 84 and 90) The evaluation of the sella in the individual cases is given in Table 16, Appendix

Re study of the films was possible in 84 cases In 21 of them the sella was extensively destroyed and could not be measured In the remaining 63 cases the means of the measurements were sellar entrance 19 8 mm (11—31 mm) length 18 5 mm (10—30 mm) and depth 13 1 mm (7—24 mm) The corresponding values for a normal sella are, according to the literature about 10, 11 and 8 mm, respectively In 2 cases (Nos 26 and 117) destructive changes were seen in the floor of the middle fossa and apex of the pyramid bone on one side

Roentgenograms taken *after treatment* were available for re study in 82 cases and in 63 cases these could be compared with those taken before treatment. Clinically obvious signs of recurrence of the tumour were the indications for

can system The calculation of disability due to visual field defects according to the American system appears to be questionable in patients with visual field defects because of scotoma

In 1927 *Kungliga Försäkringsradet* in Sweden (Royal Insurance Committee) published a table for calculation of the degree of disability due to reduction of visual acuity from accidents Application of this table has been discussed by GRANSTROM (1944) and NORDIN (1955) These authors claim that simultaneous reduction of the visual fields must naturally increase the percentage of disability Consideration must, however, also be given to other factors Exactly the same type of visual field defects can cause different degrees of disability in patients belonging to different occupations If the reduction of visual fields and visual acuity occurs suddenly, it places larger demands on the patient's power of adaptation than if gradually occurring The possibility of vocational training for some other occupation must also be considered in assessing the degree of disability The above authors stressed that, in combined reduction of visual acuity and of the visual fields, the degree of disability must be assessed individually This view is also shared by NURNBERGER & KOREY (1953)

Observations made in the present investigation corroborate the views put forth by GRANSTROM and NORDIN, with the exception that simultaneous visual field reduction does increase the degree of disability to a larger extent than that suggested by NORDIN In the present series it was found that if the visual acuity was reduced to an extent corresponding to 25—32 % disability or more, the patients were, as a rule, more or less severely disabled owing to simultaneous visual field defects It would appear that 20—25 % should be added to the values given in *Kungl Försäkringsradet*'s table for patients with simultaneous reduction of the visual fields and visual acuity, if they are to correspond well to the patient's working capacity as far as vision is concerned In the final estimation of disability, however, each case must be judged individually with due consideration to all the aforementioned factors

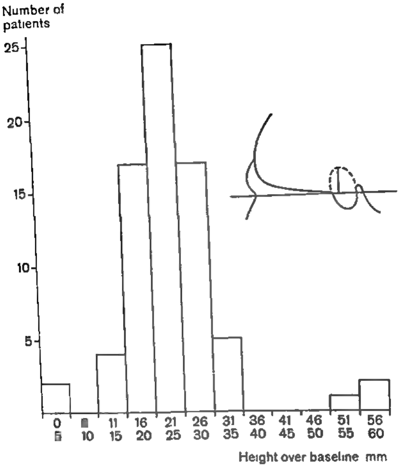

Figure 4 *Distribution of 3 patients according to height of suprasellar portion of chromophobe pituitary adenoma*

1 year later as well as re study of the old films showed further progress of a temporally expanding large adenoma The suprasellar portion at both examinations extended 29 mm above the entrance of the sella

In the remaining 12 patients of the 22 with a suspected recurrence the symptoms and signs had been vague In these patients there had occurred atypical ophthalmoneurological changes or transient minimal visual field defects visual hallucinations psychical changes or attacks of major epilepsy Four patients had had severe headache and fatigue

In 3 (Nos 71 77 and 99) of these 12 patients there was a suprasellar extension (7—12 mm) which was less extensive than before treatment In one of them

these posttreatment controls in 11 cases (Nos 14, 20, 26, 28, 29, 30, 36, 47, 56, 62 and 117) In 3 cases the roentgenographic changes were identical with those before treatment despite the recurrence, while in 1 (No 26) the destruction of the sella turcica had advanced since the pre-treatment examination In 7 cases the films showed that the entire sella turcica was extensively destroyed No pre-treatment films were available for comparison in these 7 cases

Post-treatment examinations of the sella turcica were available for re-study in 71 cases without any clinical symptoms or signs of recurrence This group included most of the 78 cases re-examined in 1960–1961 Comparison with pre-treatment films was possible in 59 of them Changes in size and structure of the sella were observed in 20 of these 59 cases Regressive changes were noted in 14 of them in 9 the sella turcica was smaller than before treatment because the dorsum sellae—upright before treatment—was tilted forward, and in 8 cases the density of the sellar region had increased Progressive changes were seen in 6 cases less density was noted in 2 of them (Nos 79 and 122) and in 4 (Nos 60, 78, 100 and 119) the deformation of the sella had increased In patient No 78 this was caused, however, by a cancer invading from the ethmoidal region As mentioned, there were no clinical signs of recurrence of the adenoma, and further radiologic examinations were not considered indicated

ENCEPHALOGRAPHIC CHANGES

Before treatment encephalography had been performed in 96 cases Of the 35 patients not examined in this way, 21 date from the period before 1946 In 2 (Nos 102 and 115) of the 96 patients the encephalograms were of normal appearance In the remaining 94 cases the records contained more or less complete descriptions of suprasellar extension The roentgen finding had been confirmed at operation in all 88 patients operated upon

Pre-treatment encephalograms of 77 patients were re-studied In 4 of them the radiologic examination had, however, been incomplete and did not allow exact evaluation

The height of the suprasellar extension of the adenoma was measured in the remaining 73 cases The results are given in Fig 4 In 59 (8 %) of the cases the suprasellar extension reached 16–30 mm above the base-line The largest adenoma (No 85) extended 60 mm above the base-line

Post-treatment encephalography had been done in 24 cases In 22 of them recurrence of the adenoma was suspected Of these 22 patients 10 (Nos 14, 26, 28 29, 30 36, 47, 56, 92 and 117) had shown strong clinical evidence of a recurrence in typical ophthalmoneurological signs of further suprasellar expansion of the adenoma In all 10 patients an adenoma was demonstrated in the encephalogram The height of suprasellar extension was considerable and varied between 22 and 45 mm One (No 117) of the 10 patients could not be regarded as having a true recurrence as the transsphenoidal operation had been incomplete Encephalographic control because of uncinate fits

visual capacity is ascribed to wide individual anatomical differences in the shape of the sella turcica and the suprasellar position of the optic chiasma and nerves (PANCOAST 1932 HENDERSON 1939 NURNBERGER & KOREY 1953, BULL 1956, MAHMOUD 1958) The effect of the tumour on ophthalmoneurologic status also varies with the direction of growth of the adenoma One of the largest adenomas with a height of 29 mm. above the sella but with mainly temporal extension had thus caused only insignificant visual disturbances (No 117)

The atrophic changes demonstrated in the 50 patients without recurrence may be due to the treatment given, *i e*, to operation and/or roentgen treatment or to degenerative changes of the tissues previously compressed by the adenoma The changes of the anterior horn of the lateral ventricle were doubtless due to the operative trauma *per se* The central changes may however have been due to atrophy of the tissues previously compressed by the adenoma The observations made will not allow any definite conclusion as to the cause of the changes

Perusal of the literature failed to reveal any reports of such central encephalographic changes These changes are, however, of interest, since it has been postulated (ARNOLD 1954 MOGENSEN 1957 and MARGUTH 1959) that roentgen treatment can injure the hypothalamus hypophyseal function and also cause psychic disorders The risk of such disorders has been used as an argument against roentgen treatment

FISCHER (1963), who studied 75 patients operated upon because of chromophobe adenoma assumed that the psychic disturbances sometimes occuring after operation may be due to operative trauma to the frontal lobe The above mentioned atrophic changes in the lateral ventricle on the operated side suggest that in some cases surgical trauma had caused permanent injury to the frontal lobe

(No 99), who had received only roentgen treatment, the height of the adenoma before treatment was 14 mm and at control after treatment it was 7 mm above the base line In the remaining 9 cases (Nos 52, 61, 63, 75, 78, 112, 113, 114 and 115) the films showed no evidence of suprasellar extension

After the control encephalography these 12 patients in whom a recurrence had been suspected, were followed up for 5 to 16 years, during which time no further clinical signs of a recurrence had appeared

In addition to the above mentioned 22 cases encephalography was made in 2 other patients (Nos 73 and 96) without clinical signs of a recurrence The aim of the examination was to control the result of treatment In one of them (No 73) the tumour had extended 35 mm above the base line before the transfrontal operation at which most of the adenoma was removed Control examination one year later showed no suprasellar extension In the other patient (No 96), in whom the operation had been limited to biopsy and who had received stereotaxic roentgen treatment, the adenoma had decreased in height from 27 to 20 mm

There were thus 14 patients in whom, in spite of certain vague symtoms, no recurrence could be demonstrated at the post treatment encephalography However, in only 4 cases was the encephalogram quite normal All the remaining 10 examinations showed considerable irregular widening of the anterior part of the third ventricle and of the suprasellar cisterns Two patients (Nos 99 and 115) had received only roentgen treatment Operation with transfrontal approach had been done in 8 patients, 7 of whom had also received roentgen treatment All these 8 patients showed changes of the anterior horn of the lateral ventricle on the operated side

COMMENTS

The importance of radiologic examinations in patients with chromophobe pituitary adenoma is evident A few points of special interest should be stressed The appearance of the sella turcica in patients with a clinically suspected recurrence was not infrequently the same as that seen at pre treatment examination On the other hand, all the patients with a clinically diagnosed recurrence showed encephalographic changes typical of suprasellar extension of pituitary adenoma

It has been stated (Huber 1956) that suprasellar expansion must reach about 20 mm before it causes any defect of the visual fields and/or visual acuity In a series comprising also some of the cases described here, Bynke & Cronqvist (1965) found that though there is a highly significant correlation between the height of the adenoma and the extent of the visual field defects, the individual variation is wide This conclusion was corroborated by the results of the present re study Twenty six patients had only incomplete bitemporal hemianopia in spite of the fact that the suprasellar portion of the adenoma had a height of on the average, 21 mm (13—29 mm) These figures agree well with Huber's (1956) The variation in the effect of the suprasellar extension of the adenoma on

In doubtful cases of hypothyroidism and adrenocortical insufficiency the effect of tentative replacement therapy was noted (SKANSE 1961, KAHANA ET AL. 1962) In a few cases, however, the data arguing for target gland insufficiency were incomplete In these cases the target gland function was classified as 'probably insufficient' a term which should thus not be interpreted as an attempt to grade the target gland insufficiency

The following symptoms and signs and laboratory studies form the basis of the evaluation of functional status of the target glands

SYMPTOMS AND SIGNS

The occurrence of amenorrhoea in pre menopausal age reduction of libido and potency reduction of facial axillary and pubic hair growth sexual undevelopment atrophy of testes The occurrence of cold intolerance, dry cold and scaly skin and myxoedema Pronounced tiredness and weakness loss of initiative inactivity, periods of sluggishness fever vomiting and hypotension possibly caused by or interpreted as due to infections and overt adrenocortical crises diagnosed in hospital

Many of these patients showed a typical more or less pronounced so-called *hypopituitary picture* This picture deserves description for it is as a whole a manifestation of pituitary insufficiency

The patient s skin is strikingly poor in pigment alabaster like areolae mammae and naevi pigmentosi are often depigmented The distribution of the subcutaneous fat resembles that of eunuchoid males The skin feels dry and cold, leathery or doughy while typical myxoedema is rare The skin of the face, especially around the mouth and eyes and of the forehead is often thin and finely wrinkled The hair on the scalp is often thin and soft, rarely dry and straggling, and the eyebrows do not often thin off laterally as in primary hypothyroidism. Previously well developed hairgrowth on the body may have been lost. Facial, axillary and pubic hair growth is often reduced, and in males the upper outline of the pubic hairgrowth is often horizontal as in females The testes are often soft or obviously atrophic In females the hypopituitary picture is conspicuous only in pronounced pituitary insufficiency

Patients with advanced hypopituitarism move slowly, speak slowly and monotonously, and they do not answer questions until after a fairly long interval They are tired they have no initiative and are indolent They have lost all ambition. They have accepted their situation and feel that 'everything is all right as it is

LABORATORY STUDIES

24 hour urinary excretion of *gonadotrophin* (*FSH*) was determined with the biological method according to GEMZELL & GEMZELL (1961) at Hormonlaboratoriet, Malmo general hospital Malmo

Basal metabolic rate (*BMR*) was determined with Krogh s spirometer and was calculated according to HARRIS & BENEDICT (1919)

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Radio-iodine test The 24 hour thyroidal uptake

CHAPTER VI

ENDOCRINE DISTURBANCES

During the period covered by the present study, i.e. 1921—1960, clinical endocrinology developed into a special branch of medicine. Particularly during the last 15 years new methods have been devised for evaluation of the function of the pituitary and of its target organs. These methods are continually being improved. The present material was therefore naturally not examined according to uniform principles.

An ideal way of studying pituitary function would be a direct assay of the various hormones produced by this gland. With the exception of gonadotrophin determination such a direct assay has been and still is unavailable for routine clinical work. Instead the clinical investigation must be devoted to the function of the target organs (gonads, thyroid gland and adrenal cortex).

In the present study the evaluation of the endocrine status of the patients before treatment had to be based on clinical symptoms and laboratory data available in the patients' records. Since the author had noticed that symptoms of insufficiency of the target organs may occur late after treatment it was decided to re-examinate the function of the target organs as late as possible after treatment. The examination was therefore based on data regarding the symptoms and signs noted at examinations performed while the patients were under observation and of the findings made in the patients still living at the time of the re-examination. For several reasons it was necessary to limit the number of laboratory tests at the re-examination.

All data about the function of the target organs in the individual patients are given in Table 17 in the Appendix. These data thus describe the patient's status before treatment of the tumour and as late as possible in the observation period after treatment.

In what follows interest is focused mainly on the group of patients treated with transfrontal operation and a standardized type of medium voltage roentgen therapy.

METHODS

PRINCIPLES OF CLINICAL EVALUATION OF TARGET GLAND FUNCTIONS

Each case was evaluated on the basis of anamnestic and bedside data as well as on the results of laboratory studies

In doubtful cases of hypothyroidism and adrenocortical insufficiency the effect of tentative replacement therapy was noted (SKANSE 1961, KAHANA ET AL. 1962) In a few cases, however the data arguing for target gland insufficiency were incomplete In these cases the target gland function was classified as "prob ably insufficient a term which should thus not be interpreted as an attempt to grade the target gland insufficiency

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Table 8 *The gonadal function as reflected by menstrual periods in 13 pre menopausal female patients with chromophobe pituitary adenoma before and after treatment with transfrontal operation and uniform medium voltage radiation*

o = no insufficiency (+) = probable insufficiency + = firm insufficiency

Gonadal function	Before treatment	After treatment o	After treatment (+)	After treatment +
	Number of patients	2	0	11
o	2	1		1
(+)	0			
+	11	1		10

menopausal age at the time of treatment and none of these were then judged as having primary ovarian failure These 13 patients are accounted for in Table 8 One of them (No 95) had normal menstruations both before treatment and at the time of re examination—she was then 41 years old One woman (No 129) in whom the disease made its first appearance during pregnancy, had persistent amenorrhoea after treatment Because of the patient's interesting history this case is described below A detailed discussion of the case has been published by ENOKSSON ET AL (1961)

Towards the end of each of 2 pregnancies at an interval of 4 years this patient (No 129) experienced reduction of visual fields and visual acuity On both occasions parturition had to be provoked Her vision became normal spontaneously 3 weeks respectively 5 months after parturition Menstruation returned 1 5 years after the first parturition but after the next one ammenorrhoea persisted At the end of the first pregnancy and a short time afterwards the patient had diabetes insipidus with a urine output of 5 8 liters a day No other disturbances could be demonstrated The patient was operated upon for a moderately large cystic adenoma half a year after the second parturition and she received roentgen treatment with a tumour dose of 3 000 r/22 days

Of the above mentioned 13 women in pre menopausal age in this treatment group 11 had amenorrhoea since, on the average, 30 years of age (range 17—42) In 1 woman (No 84) who had had amenorrhoea for 1 year before the operation menstruation returned 2 months after the operation and after a further month she became pregnant During a short time after the operation her libido was pathologically increased Menstruation did not return in any of the other 10 women who were in pre-menopausal age at the time of treatment Thus, both before and after treatment 11 of these 13 women had amenorrhoea of presumably pituitary origin

Of the remaining 15 women in this treatment group 2 were operated upon in pre menopausal age 1 (No 76) of them was amenorrhoic because of primary ovarian disease (large cystic ovaries), 1 (No 105) was a case of Turner's syndrome Two patients (Nos 69 and 127) had been subjected to hysterectomy in pre-menopausal age The other 11 women

and urinary excretion was measured by conventional scintillation technique

Four hour water load test was done according to LUFT & SJOGREN (1953)

Four hour ACTH test was performed according to THORN (1951)

Insulin tolerance (ITT) was performed according to FRASER, ALBRIGHT & SMITH (1941) and *blood sugar* according to HAGEDORN, HALSTROM & JENSEN (1935)

24 hour urinary excretion of *17 ketosteroids (17 KS)* and *17 ketogenic steroids (17 KGS)* was determined according to ZIMMERMANN (1935) as modified by JENSEN & TOTTERMAN (1952) respectively according to BROOKS & NORTHBERSKI (1953) These determinations were made at the Hormonlaboratoriet, Malmo general hospital Malmo The normal values at this laboratory for various ages and for each sex have been reported by JENSEN (1961)

Plasmacorticosteroid determinations were performed by the fluorimetric method of GUILLEMIN, CLAYTON & LIPSCOMB (1958), slightly modified by HEDNER (1961)

COMMENTS

In some previously published series of patients with chromophobe pituitary adenoma the occurrence of target gland insufficiency, single symptoms or signs and the results of certain laboratory tests have been reported (YOUNGHUSBAND ET AL 1952, MOGENSEN 1957, HEIMBACH 1959, FISCHER 1963) Only in a few publications have attempts been made at a differentiated evaluation of the various target gland functions in the individual patient (NURNBERGER & KOREY 1953) In the present investigation the function of the target glands was based on an all round evaluation of all available data in the individual cases From 1954 the investigation of the endocrine status of the patients were performed according to largely uniform principles

Only exceptionally were the radioiodine tests performed at the same time as the PBI-determinations as the latter method was not introduced in the investigation of these patients until 1958—1959 It should also be pointed out that the corticotrophin test with simultaneous determination of the urinary steroid excretion was used only in about 10 cases of the present material and even then by different techniques, so that the results are difficult to evaluate

The programme set up for re-examination of the 70 hospitalised patients included the following laboratory studies determination of the 24-hour urinary excretion of FSH, 17-KS and 17-KGS, serum cholesterol, BMR, PBI, water load test, ITT These determinations were made in most of the 70 cases Towards the end of the re-examination determination of plasmacorticosteroids could be added to the programme The diurnal variation was studied in 21 patients After the re examination many of the patients could be followed-up for 1—2 years The target gland function in patients with probable insufficiency could thus be controlled as well as the effect of replacement therapy instituted at the re-examination

GONADAL FUNCTION

COMBINED TREATMENT (OPERATION AND ROENTGEN TREATMENT)

TRANSFRONTAL APPROACH AND RADIATION WITH UNIFORM MEDIUM VOLTAGE TECHNIQUE

Gonadal function in the females Of the 28 females in this group 13 were in pre-

never able to pass the left when walking The patient was 45 years of age when first seen at the orthopaedic clinic She was operated upon and could then walk fairly well Besides this deformity of the hips the patient had pronounced kyphoscoliosis so that it was difficult to form a definite opinion of her bodily proportions but she may perhaps be regarded as an unusual case of female eunuchoidism

In patient No 90 as in patient No 129 mentioned above the visual fields and visual acuity rapidly decreased towards the end of the first pregnancy and she had transient diabetes insipidus Ten days after partus provocatus she was operated upon for a moderately large cystic pituitary adenoma She received no roentgen therapy Menstruations returned 4 months after parturition A second pregnancy 5 years later was uncomplicated At the re examination she showed no signs of endocrine insufficiency

COMMENTS

Menstrual disorders and amenorrhoea in patients with chromophobe pituitary adenoma may be regarded as evidence of pituitary insufficiency unles primary ovarian insufficiency can be demon strated It is, however, always difficult to ascertain the cause of amenorrhoea in women aged 40—50 years in wich deca de manifestations of the expanding chromophobe adenoma often occur It is therefore difficult to accept the conclu sion of BAKAY (1950) and HEIMBACH (1959) that amenorrhoea occurring below the age of 50 in women with pituitary adenoma is always due to pituitary insufficiency Each case must be judged individually

In chromophobe pituitary adenoma *bilateral testicular atrophy* is a definite sign of hypopituitary hypogonadism This is accompanied by reduction or loss of sex hair growth In the present series of 131 patients, 42 men were judged as having hypogonadism before treatment Testicular atrophy with loss of libido and potency was noted in 33 (79 %) of them The remaining 9 could date the loss of libido and potency in such a way that it could be ascribed to pituitary insufficiency In 3 of them testicular atrophy supervened after treatment Reduced libido and potency not certainly related to pituitary insufficiency occurred in 7 men On the other hand there were also 3 men (Nos 31, 77 and 94) with preserved libido and potency despite testicular atrophy Such observations like pathologically increased libido after operation (No 84) show that these functions are not entirely hormone-dependent (FISCHER 1963, LINDQUIST 1960 and 1965)

Determination of the 24 hour *excretion of FSH in the urine* may be of value in the investigation of patients with chromophobe adenoma Low or undetectable gonadotrophins is a common finding in women with chromophobe adenoma and amenorrhoea in pre menopausal age Low values are also often seen in women in whom the adenoma makes its first appearance after the ordinary menopause (KLINEFELTER ALBRIGHT & GRISWOLD 1943 VAN ARSDELL & WILLIAMS 1956, JENSEN 1963) In primary ovarian disease the FSH is high usually far above 40 MUU (FLUHMANN 1944 HELLER & SHIPLEY 1951 JOHNSEN 1959, JENSEN 1963)

In the present series low (FSH > 10 < 40 MUU) or no detectable (< 10 MUU) gonadrotrophin was found before treat ment in 6 of 7 women and after treat-

Table 9 *The gonadal function in 42 male patients with chromophobe pituitary adenoma before and after treatment with transfrontal operation and uniform medium voltage radiation*

0 = no insufficiency, (+) = probable insufficiency + = firm insufficiency

Gonadal function (Before treatment)		After treatment 0	(+)	+
	Number of patients	18	1	23
0	25	18	1	6
(+)	4			4
+	13			13

were operated upon in post-menopausal age after ordinary menopause

Determination of the urinary excretion of gonadotrophin was made in only 2 women both before and after treatment In patient No 66 the FSH excretion was less than 40 MUU, and in patient No 76 it was more than 40 MUU The same results were obtained in both cases before treatment as well as at the re-examination FSH was determined in a further 8 cases at the re-examination In 3 of them there was no detectable gonadotrophin and in 5 the FSH excretion was > 10 < 40 MUU

The investigation thus showed evidence of insufficiency of the gonadotrophic function after treatment in at least 20 of the 28 women in this group

Gonadal function in the males In 42 of the 50 men in this group it was possible to compare gonadal status (according to reduction of libido and potency, testicular atrophy, sex hair reduction) before and after treatment (Table 9) Before treatment gonadal status was normal in 25 men (60 %) but insufficient in 17 (40 %) After treatment signs of gonadal insufficiency supervened in a further 7 cases Some evidence of gonadal insufficiency were thus present after treatment in all together 24, *i e* 57 % of the 42 men In none of the men did gonadal function become normal after treatment

OTHER TREATMENT GROUPS

Gonadal function could be compared in the other treatment groups before and after treatment in 14 women and 20 men But each treatment group included only a few patients of each sex, so that comparison cannot be made between the treatment groups concerning the effect of tumour treatment on gonadal function

Here only 2 cases of particular interest will be briefly mentioned

In patient No 10 visual defects occurred at 15 years of age and she had occasional menstruations at 16 years The diagnosis of chromophobe adenoma was made when the patient was 17 years and roentgen treatment was given Between the age of 21 and 25 bilateral epiphysiolysis of the hip joints occurred Roentgen examination showed that the epiphyseal lines were still open in both knees and in the skeleton of the hands Her sex characters were undeveloped Because of extreme varus of the hips the patient s legs were crossed and the right leg was

5 000 r/175 days Thyroid substitution treatment was not given but the BMR increased to about −10 % during the first few years after treatment At the re-examination 9 years after treatment the patient had no clinical symptoms of hypothyroidism, the BMR was −11 % and the PBI 4 7 µg/100 ml

From available data in this group it may thus be concluded that among the 56 patients in whom thyroidal function could be judged both before and after treatment signs of hypothyroidism were noted in all together 13 (23 %) patients before treatment and in 22 (39 %) after treatment Of all the 68 cases in this treatment group in which thyroidal function could be judged after treatment 28 (41 %) had hypothyroidism

OTHER TREATMENT GROUPS

The thyroidal function could be compared before and after treatment in only few cases in each of the small treatment groups The effect of tumour treatment on thyroidal function could therefore not be compared between these groups and the above discussed large treatment group

COMMENTS

More or less severe *cold intolerance* occurred in those patients considered to have hypothyroidism But this symptom also occurred in 9 patients (Nos 57 67 70 75 111 118 123 124 and 126) in whom thyroidal function was certainly normal In 4 (Nos 67 75 111 and 123) all with severe adrenocortical insufficiency the cold intolerance disappeared after institution of cortisone substitution Similar observations have been reported by Oberdisse (1957)

True *myxoedema* is rare in patients with chromophobe pituitary adenoma (Nurnberger & Korey 1953 Peters et al 1954, Wayne 1960) Of all the patients in the present series 36 had hypothyroidism with certainty Only 6 (Nos 32, 41, 44, 69, 85 and 96) had clinically overt myxoedema

The investigation showed that even a considerable decrease of the *BMR* values need not imply thyroid insufficiency It must however be pointed out that the BMR in healthy Swedish subjects according to Wising (1934) and Hamberger & Lundgren (1965) is low −6 3 to −8 8 %, compared with the standard of Harris & Benedict (1919) In the present series thyroidal function was judged as normal in 71 patients before and in 46 after treatment In 19 respectively 13 of these cases BMR was −15 % or lower There were also a few cases in whom the BMR persisted at a level below −15 % despite presumably adequate substitution for thyroid and/or adreno-cortical insufficiency Such a low BMR has also been described previously in patients with pituitary insufficiency (Younghusband et al 1952, Nurnberger & Korey 1953 Skanse 1953 and 1961, VanArsdell & Williams 1956) A low BMR that cannot be attributed to thyroidal insufficiency has been described as due to lack of somatotrophic hormone (Skanse 1961 a 1961 b, Falkheden 1962, Ikkos & Luft 1963)

The diagnostic value of *serum cholesterol* in hypopituitary hypothyroidism is discussed (Younghusband et al. 1952, Nurnberger & Korey 1953 Peters et al 1954 Skanse 1961 a) In the

Table 10 *The thyroidal function in 56 patients with chromophobe pituitary adenoma before and after treatment with transfrontal operation and uniform medium voltage radiation*

o = no insufficiency (+) = probable insufficiency + = firm insufficiency

Thyroidal function	Before treatment: Number of patients	After treatment: o	(+)	+
Number of patients		34	3	19
o	43	33	2	8
(+)	4		1	3
+	9	1		8

ment in 20 out of 22 women with amenorrhoea in pre-menopausal age or after ordinary menopause FSH excretion of more than 40 MUU was found only in 1 patient (No 76) who had primary ovarian disease and in one 79 year old woman (No 39)

Absence of gonadotrophin is also common in men with chromophobe pituitary adenoma (KLINEFELTER, ALBRIGHT & GRISWOLD 1943) Of 29 men with hypogonadism in the present series laboratory examination revealed no detectable FSH in 23, including 16 with testicular atrophy The FSH level found must, however, be judged with caution since wide individual variations can occur (ALBERT 1960, DANOWSKI 1962)

Determination of the 17-KS in the urine is of little diagnostic value in hypopituitary hypogonadism This is natural since also in man only one third to one fourth of the 17-ketosteroids derive from the testes (LORRAINE 1958, PAULSEN 1962) In this series low values of 17-KS occurred only in cases with testicular atrophy co-existing with advanced adrenocortical insufficiency

THYROIDAL FUNCTION

COMBINED TREATMENT (OPERATION AND ROENTGEN TREATMENT)

TRANSFRONTAL APPROACH AND RADIATION WITH UNIFORM MEDIUM VOLTAGE TECHNIQUE

Of the 69 cases in this group it was possible to compare thyroidal function in 56 patients before and after treatment (Table 10) Before treatment thyroidal function was normal in 43 (77 %) of these patients After treatment signs of hypothyroidism appeared in 10 of these 43 patients There was probable hypothyroidism before treatment in 4 patients Three of them had evident thyroidal insufficiency after treatment Of 9 patients with a well established diagnosis of hypothyroidism before treatment thyroid function had become normal in one (No 66) by the time of the re examination

Before treatment patient No 66 had pronounced cold intolerance—she was then 57 years This symptom disappeared for some weeks in association with a thyrotrophin test at which an increase of the BMR was noted from −27 % to −4 % (Examination by Docent B Skanse 1952) Postoperative roentgen treatment was given with a tumour dose of

Table 11 *The adrenocortical function in 45 patients with chromophobe pituitary adenoma before and after treatment with transfrontal operation and uniform medium voltage radiation*
o = no insufficiency (+) = probable insufficiency, + = firm insufficiency

	Before treatment	After treatment		
Adrenocortical function		o	(+)	+
	Number of patients	23	4	18
o	28	22	3	3
(+)	6	1	1	4
+	11			11

pituitary hypothyroidism the PBI values may sometimes fall within the normal range. Repeated control examinations should therefore be done before substitution therapy is tried.

Findings at the re-examination confirm the conclusion by previous authors (NURNBERGER & KOREY 1953, OBERDISSE 1957, WAYNE 1960, SHEEHAN 1961, SKANSE 1961 a, 1961 b, FALKHEDEN ET AL. 1962) that the diagnosis of pituitary hypothyroidism may often be difficult because the deficiency of thyrotrophin is rarely complete and because the clinical picture is often confusing owing to simultaneous deficiency of other pituitary hormones. It must be emphasized that a low BMR alone is insufficient evidence of hypothyroidism. PBI determinations are of greater diagnostic value. The diagnosis must however be based on a critical analysis of the anamnestic symptoms, bedside observations and laboratory findings. In some cases the response to substitution therapy must decide the question as pointed out above all by SKANSE (1961 a) and KAHANA ET AL. (1962).

ADRENOCORTICAL FUNCTION

COMBINED TREATMENT (OPERATION AND ROENTGEN TREATMENT)

TRANSFRONTAL APPROACH AND RADIATION WITH UNIFORM MEDIUM VOLTAGE TECHNIQUE

Comparison of adrenocortical function before and after treatment was possible in 45 of the 69 patients in the group (Table 11). In 28 (62 %) of these 45 patients the function was normal before treatment but in 6 of them it became insufficient after treatment. There was more or less strong evidence of adrenocortical insufficiency in 17 (38 %) of the patients before treatment. One patient (No. 89) probably had adrenocortical insufficiency before treatment (pronounced tiredness, severely pathologic water load test) but half a year after treatment there were no subjective and objective signs of insufficient adrenocortical function. After treatment adrenocortical function was normal in 23 (51 %) and insufficient in 22 (49 %) of these 45 patients. In the whole group adrenocortical function could be evaluated after

present series the serum cholesterol varied widely from one occasion to another in one and the same patient. At the re-examination, when the cholesterol was determined under fairly uniform conditions, the mean value found for 46 euthyroid patients was 287 mg/100 ml (range 192—372) and in 35 with evident hypothyroidism it was 297 mg/100 ml (range 114—477). Two of the highest values, 434 and 477 mg/100 ml respectively, were found in 2 patients (Nos 44 and 96) with hypothyroidism and myxoedema. The observations in this series do not, however, permit any conclusions about the values of serum cholesterol and the patients' endocrine status.

The radio—iodine test was done in 17 cases before, and in 46, after treatment. With but few exceptions only the 24 hour thyroidal uptake and urinary excretion were determined. Thus, no determinations were made of the 24—48-hour excretion which is of great diagnostic value in hypothyroidism (SKANSE 1949, FRASER 1956, BLOM 1954, STRANGE 1959). Twenty-five patients with clinical evidence of hypothyroidism were examined with the radio-iodine test. Only 2 (Nos 94 and 102) of these patients had a low thyroidal uptake (11 and 7 % respectively) and in all the other patients there was a thyroidal uptake above 20 %. Both regarding the thyroidal uptake and urinary excretion the values showed a wide range of variation with roughly even distribution between hypothyroid and euthyroid cases. No definite correlation was found between the clinical picture and the results of the radio-iodine test.

It was surprising to find that the 24-hour uptake showed no consistent covariation with the clinical or laboratory findings. The high radio-iodine uptake also in cases with clinically well documented hypothyroidism may be due to iodine deficiency and a certain persistent thyrotrophin activity (WERNER ET AL. 1950, BLOM 1954, OWEN ET AL 1955, VANARSDELL & WILLIAMS 1956, STRANGE 1959). According to BLOM, iodine deficiency often occurs in patients with hypopituitarism. This relatively high radio iodine uptake must be regarded as a sign of some degree of preserved thyrotrophin production (LI ET AL 1955, SKANSE 1961).

The serum protein-bound iodine was determined in 13 cases before treatment and in 57 after treatment, mostly at the time of the re-examination 1960—1961. In 22 patients with clinical evidence of hypothyroidism the PBI was 2.4—6.4 µg/100 ml. Values above the lower limit of the normal range of variations, *i.e.* over 3.8 µg/100 ml, were noted in 2 cases (Nos 31 and 72) with probable thyroidal insufficiency as well as in 6 other cases (Nos 71, 77, 100, 115, 122 and 130), where the diagnosis could be regarded as reasonably well documented by other observations, particularly the result of substitution treatment.

A low PBI is generally accepted as a fairly reliable index of both primary and secondary hypothyroidism (PETERS ET AL 1954, LI ET AL 1955, SKANSE 1961 a, FALKHEDEN 1962). It has, however, been pointed out by SKANSE (1961 a) that in

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Adrenocortical function	Before treatment	After treatment		
		o	(+)	+
	Number of patients	23	4	[illegible]
o	28	22	3	3
(+)	6	1	1	4
+	11			11

pituitary hypothyroidism the PBI values may sometimes fall within the normal range Repeated control examinations should therefore be done before substitution therapy is tried

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treatment in 67 patients and it was found insufficient in 30 (45 %)

OTHER TREATMENT GROUPS

Of the patients belonging to these groups, comparison between adrenocortical function before and after treatment was possible in only 11 It is therefore impossible to make any comparison between the treatment groups concerning the effect of tumour treatment on adrenocortical function In one man (No 119) pronounced tiredness had been noted before treatment as well as repeated pathologic water load tests, severe hypoglycaemic unresponsiveness in insulin tolerance tests and low excretion of 17-KGS After treatment (transsphenoidal operation and radiation) the patient was symptomfree and the results of the laboratory tests had become normal

COMMENTS

The importance of thorough investigation of adrenocortical function in patients with chromophobe pituitary adenoma cannot be overemphasized (SHEEHAN & SUMMERS 1949, NURNBERGER & KOREY 1953, KOEPFF & VIEILLARD 1954, CAUGHEY & GARROD 1955, SKANSE & MIOBNER 1959, SCHWARZ 1962) In the present study more or less severe disabling tiredness and weakness were noted after treatment in 34 of the 40 patients with an established diagnosis of adrenocortical insufficiency, which symptoms were relieved by cortisone replacement therapy There were 4 cases (Nos 67, 69, 74 and 92) with severe adrenocortical crisis with a fatal outcome in 1 (No 74)

Physical examination of the patients in the series revealed little or nothing suggesting adrenocortical insufficiency except in patients with pronounced hypopituitarism Even a blood pressure of 180/90 was noted in 1 patient (No 67) with adrenocortical crisis soon after that (cfr SHEEHAN & SUMMERS 1949, OELBAUM 1952, JEFFERSON 1957) A full-blown hypopituitary picture nearly always means that the patient has adrenocortical insufficiency Marked reduction or loss of sex hair growth was noted in all of these cases In 2 women (Nos 86 and 88), however, aged 58 and 68 years, practically all the axillary hair and the pubic hair disappeared soon after treatment in spite of the fact that they had no signs of target gland insufficiency ALBRIGHT, SMITH & FRASER (1942) and VAN WYK (1962) thought that the sex hair growth in women is stimulated only by adrenocortical androgens but the ovarian hormone probably also plays some role since sex hair growth is not, as a rule, reduced in primary adrenocortical insufficiency (Addison's syndrome) in women

Below, the value of certain widely used function tests are discussed on the basis of experience made in the present series

A normal *four-hour water load test* argues strongly for intact adrenocortical function (LEFT & SJOGREN 1953, and others) In the present series, however, there was one patient (No 117) with a normal water load test but with severe hypoglycaemic unresponsiveness in ITT, which might argue for partial insufficiency of the adrenal cortex (PASCHKIS

& CANTAROW 1951, OBERDISSE 1957) Many authors have stressed that the water load test has several sources of error and warning voices have been raised against the risk of water intoxication (CALGHEY & GARROD 1954 OBERDISSE 1957 THORN 1959 CHRISTY 1960 HOVEID 1961) No such complications had ever been noted in the present series possibly because the water load was rather small compared with the amounts advocated by ROBINSON, POWER & KEPLER (1941) and SOFFER & GABRILOVE (1952) But for the above exception all cases of clinically certain adrenocortical insufficiency in this series showed reduced excretion and dilution power at the water load test In most of the patients the test became normal after institution of cortisone Provided the test is properly performed and its results are properly interpreted, the water load test is still useful as a diagnostic aid in cases of suspected adrenocortical insufficiency

Thorn's eosinophil test was used in the present clinical material for only a few years in the beginning of the 1950s Is it nowadays regarded as a method of doubtful specificity with many methodological errors (LUFT & SJOGREN 1953 HERRMANN 1955 FRAWLEY 1956, BIRKE, DICZFALUSY & PLANTIN 1958 KRUSIUS 1960 ARNER ET AL 1963) Its drawbacks were repeatedly experienced also in the present study

The insulin tolerance test (ITT) according to FRASER, ALBRIGHT & SMITH (1941) had been performed in a large proportion of the cases and was therefore also included in the re-examination Owing to the considerable risk of adrenocortical crisis in pronounced hypoglycaemic unresponsiveness (WHITTAKER & WHITEHEAD 1954 CALGHEY & GARROD 1955, CHRISTY 1960) the ITT was however, not performed in cases where adrenocortical insufficiency was thought to be very severe

The ITT was performed in 26 cases with normal adrenocortical function and in 19 cases in which adrenocortical insufficiency had been diagnosed on clinical grounds the results of the determinations of the urinary and plasma steroids and of the water load tests

Fig 5 shows the fall in the blood sugar level from that noted before the injection In the group of patients in whom adrenocortical function was judged as normal the shape of the mean blood sugar curve after the injection of insulin resembled that of a corresponding curve in a series of normal subjects (ARNER, HEDNER & KARLEFORS 1962)

In the group of patients with adrenocortical insufficiency, however the blood sugar curve was substantially lower than in the group of patients with normal function. The difference was statistically significant ($P < 0.01 - P < 0.001$) for all determinations between 30 and 90 minutes after the injection of insulin

In the present series the insulin tolerance test did not prove very informative in the diagnosis of adrenocortical insufficiency Only in 6 (Nos 50, 100 117, 119, 120 and 122) of the 19 patients with adrenocortical insufficiency was the blood sugar level between 30 minutes and 120 minutes below the mean value *minus* 2 SD in the group with normal adrenocortical function Judging from

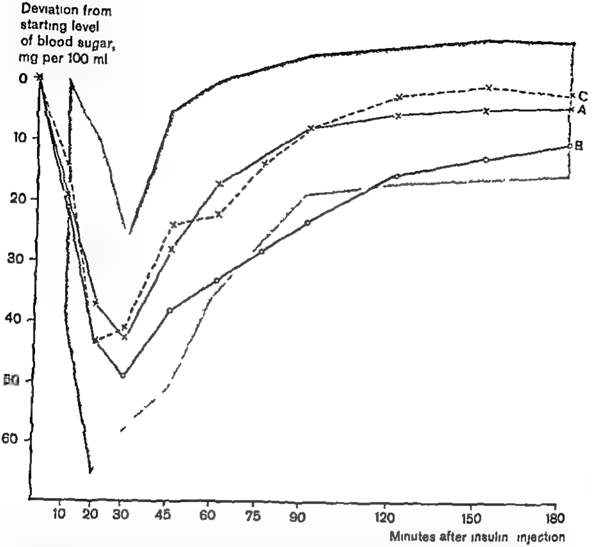

Figure 5 Results of insulin tolerance test (Fraser Albright & Smith 1941) *in patients with chromophobe pituitary adenoma mean blood sugar level ± 2 Standard Deviations in 26 patients with normal adrenocortical function A and in 19 patients with adrenocortical insufficiency B compared with ITT in 10 healthy subjects* C (Arner Hedner & Karlefors 1961)

other observations, these 6 patients appeared to have more severe adrenocortical insufficiency than the remaining 13 patients in the group In patients with clinically moderate insufficiency, then, the *ITT* produced no conclusive evidence Paschkis & Cantarow (1951), Oelbaum (1952) and Whittaker & Whitehead (1954) found the results of insulin tolerance tests to be normal in some of the patients whom they from other findings thought to have adrenocortical insufficiency

Determination of the 24-hour urinary excretion of *17-KS* and *17 KGS* is believed to be useful in the investigation of adrenocortical function in patients with chromophobe pituitary adenoma

Table 12 *Diurnal variations of plasma corticosteroids in 21 patients treated for chromophobe pituitary adenoma 14 patients with normal and 7 with insufficient adrenocortical function*

Pat No	Sex age	Plasma corticosteroids µg per 100 ml plasma 08	12	16	20	24	04	08	17 KS	17 KGS	Water load test	ITT
					A Patients with normal adrenocortical function							
16	M 61	20 1	17 9	13 4	13 4	11 2	13-4	17 9	2 9	13 5	■	o
35	M 36	13 7	16 5	19 4	17 2	16 0	16 0	17 2	17 4	15 2	+	
39	F 79	26 1	22 7	11 3	14 7	13 6	15 9	27 3	5 6	10 8	⊥	
53	M 67	24 2	18 5	11 6	10 4	13 9	10-4	20 9	12 7	15 9	o	o
56	M 33	13 2	20 4	19 2	9 6	7 2	20 4	31 2	10 4	16 7	o	
66	F 67	21 7	9 1	12 5	11 4	8 0	11 4	19.4	1 1	7 0	⊥	o
80	F 28	13	11	12	7	9	29		6 8	15 6	o	o
88	F 72	22 9	19 4	18 3	14.9	11-4	14 9	21 7	5 8	8 2	⊥	
90	F 33	15 0	18.4	18 4	19 6	15 0	12 7	13 8	15 2	22 6	o	o
93	F 58	19 0	16 8	14 5	16 8	15 6	23 4	32 4	1 9	6 1	■	■
106	M 70	19	15	12	10	8	19	21	8 3	10 2	o	o
107	F 58	23 5	16 0	16 0	19 2	12 8	13 9	33 1	5 3	16 0	⊥	o
110	F 49	26 3	21 9	16 5	14 3	11 0	28 5	20 8	2 4	7 8	■	
129	F 29	19 1	10 8	13 1	6 0	6 0	9 6	16 7	7 7	16 0	o	o
Mean		19 8	16 8	14 9	13 2	11 3	16 5	22 6				
S D		4 6	4 1	3 0	4 3	3 3	5 4	6 4				
					B Patients with adrenocortical insufficiency							
24	F 75	9 3	6 0	9 5	6 0	9 3	10 7	10 7	3 6	4 9	o	o
42	M 75	12 4	7 9	6 8	7 9	6 8	6 8	9 1	0 4	3 3	⊥	
67	F 63	4 6	4 6	4 6	4 6	3 3	2 3	2 3	0 5	2 0		
100	M 58	10 1	5 5	12 3	11 2	6 7	8 9	15 7	1 7	5 6	—	⊥
115	M 37	10 7	7 5	9 6	8 5	6 4	7 3		8 0	10 7	⊥	
121	M 62	14 7	4 9	4 9	3 7	7 3	9 8	11 0	2 7	8 0	⊥	o
130I	M 68	6 8	6 8	6 8	6 8	4 3	5 7	5 7	2 0	3 5	—	
130II	68	13 2	13 2	10 7	11 9	10 7	10 7	11 9				
Mean		10 2	7 0	8 2	7 6	6 9	7 8	9 3				
S D		3 3	2 8	2 8	2 9	2 4	2 9	4 4				
					C Healthy subjects (mean values of 12 individuals)							
Mean		21 8	18 1	14 5	10 8	9 1	22 7	23 7				
S D		5 2	4 6	4.7	4 2	2 2	8 1	4 3				

Determination of the 17 KG is more important than that of 17 KGS (JENKINS ET AL 1955 BIRKE, DICZFALUSY & PLANTIN 1958) In this series the excretion of 17 KGS was however normal in repeated determinations in 15 out of 41 patients with adrenocortical insufficiency after treatment It has been stressed that in moderate reduction of the adrenocorticotrophic function of the pituitary this function is under basic conditions sufficient to maintain a normal excretion of adrenocortical steroids (LEVELL ET AL 1957, LIDDLE ET AL 1959 HOKFELT &

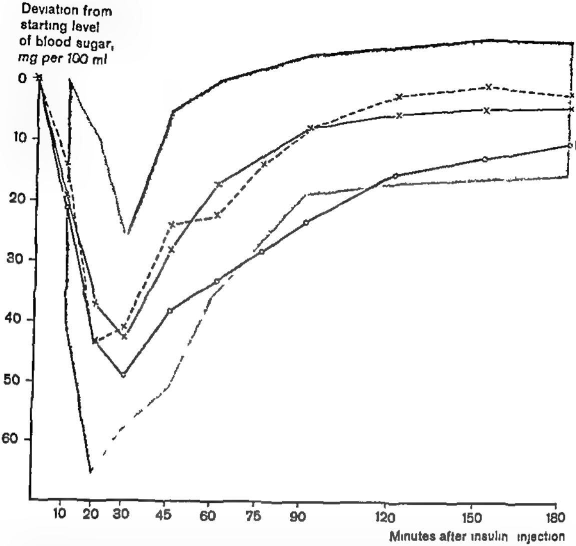

Figure 5 *Results of insulin tolerance test* (FRASER ALBRIGHT & SMITH 1941) *in patients with chromophobe pituitary adenoma mean blood sugar level* ± *2 Standard Deviations in 26 patients with normal adrenocortical function, A and in 19 patients with adrenocortical insufficiency B compared with ITT in 10 healthy subjects* C (ARNER HEDNER & KARLEFORS 1961)

other observations, these 6 patients appeared to have more severe adrenocortical insufficiency than the remaining 13 patients in the group In patients with clinically moderate insufficiency, then, the ITT produced no conclusive evidence PASCHKIS & CANTAROW (1951), OFLBAUM (1952) and WHITTAKER & WHITEHEAD (1954) found the results of insulin tolerance tests to be normal in some of the patients whom they from other findings thought to have adrenocortical insufficiency

Determination of the 24 hour urinary excretion of *17-KS* and *17-KGS* is believed to be useful in the investigation of adrenocortical function in patients with chromophobe pituitary adenoma

sufficiency was always significantly lower ($P < 0.01 - P < 0.001$) than in the group of patients considered to have normal adrenocortical function With the exception of the values noted at 8 p m and midnight it was also significantly lower than the values in the group of healthy subjects

In all the individual patients with obvious adrenocortical insufficiency the values for plasma corticosteroids in 2—6 determinations out of 7 were considerably lower ($P < 0.05$) than corresponding mean values in healthy subjects The results of plasma corticosteroid determinations corresponded well to the clinical evaluation

In 1 case (No 130) the water load test was strongly pathological the excretion of steroids in the urine was low and the patient complained of severe fatigue for half a year after the operation and roentgen therapy Three months after the end of tumour treatment the plasma corticosteroid level was low but at follow up 3 months later it was normal On neither occasion was there any diurnal variation The patient felt better but he was judged as having moderate adrenocortical insufficiency and he was given cortisone replacement therapy with a satisfactory clinical effect According to STEINBECK (1959) a normal plasma corticosteroid level may sometimes occur in the presence of moderate adrenocortical insufficiency and the urinary excretion of steroids may also be normal

The absence of diurnal variation of the plasma corticosteroids in patients with chromophobe pituitary adenoma may be due to a disorder of the regulation of diurnal rhythm by the hypothalamus caused by the expanding adenoma (HOKFELT & LUFT 1959) Of the 22 patients in whom the plasma corticosteroids were determined after treatment all except 1 (No 115) had had adenomas with suprasellar extension reaching on the average, 23 mm (12—31 mm) over the entrance of the sella in the encephalograms Among the 14 patients with normal adrenocortical function all had a normal plasma corticosteroid level and all but 2 (Nos 35 and 90) had normal diurnal variation

It is evident from the present investigation that the diagnosis of adrenocortical insufficiency in chromophobe pituitary adenoma is often difficult The diagnosis should be based on a wide variety of symptoms and signs and laboratory tests Repeated examinations of the patient are often necessary and tentative substitution therapy *must often* be resorted in order to decide the diagnosis Determination of the basic 24 hour curve of the plasma corticosteroids would seem to be valuable Functional tests with simultaneous determination of the plasma corticosteroids will in future probably yield useful information in the diagnosis of disorders of the hypophyseal adrenocortical system

TOTAL TARGET GLAND STATUS

The effect of tumour treatment on the function of individual target glands was described above In order to form an opinion of the effect of treatment on the entire glandotrophic function of the pituitary it was considered of interest to study the extent of total target gland insufficiency in the individual cases It was possible to compare the total gland status before and after treatment in 38

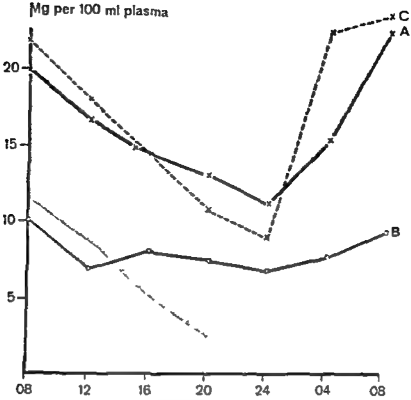

Figure 6 *Diurnal variation of plasma corticosteroids in patients with chromophobe pituitary adenoma mean values in 14 patients with normal adrenocortical function A and in 8 patients with adrenocortical insufficiency B compared with the mean values —2 Standard Deviations in 12 healthy subjects C*

LUFT 1959, SOLEM & BRINCK-JOHNSON 1961) The ability to increase the activity of the hypophyseal-adrenocortical activity in stressful situations is, however, markedly reduced in such patients But the adrenal cortex still responds fairly well to exogenous ACTH In patients with moderate pituitary insufficiency, then, neither determinations of the urinary steroid excretion nor corticotrophin tests are of diagnostic help, an observation amply confirmed by the present investigation The results may even give misleading information (HAYES & KUSHLAN 1956, ABU HAYDAR ET AL 1958, BIRKE, DICZFALUSY & PLANTIN 1960, SJOGREN 1962)

The level and diurnal variation of *plasma corticosteroids* were determined in 21 of the 70 hospitalised patients [1] On the basis of other observations adrenocortical function was judged as normal in 14 of them, but as insufficient in the remaining 7 patients (Table 12) In 1 (No 130) of the latter patients determinations were made on 2 occasions

The mean diurnal *level* of plasma-corticosteroids in the group with normal adrenocortical function did not differ from the mean values of a group of healthy subjects (Fig 6) On the other hand, the corresponding mean values in the group with adrenocortical in-

[1] I wish to thank Dr P Hedner for valuable help with the determination of the plasma corticosteroids and the statistical calculations

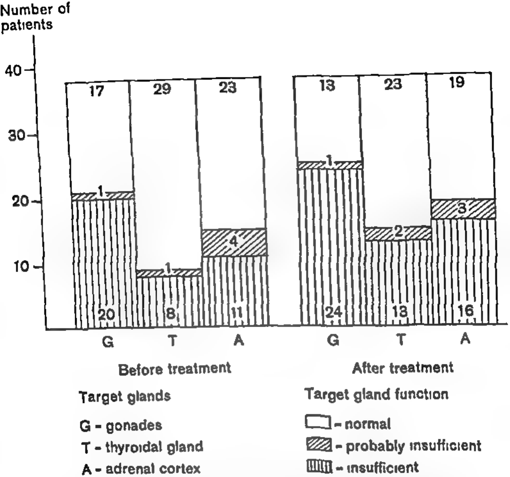

Figure 7 — *Thirty-eight patients treated for chromophobe pituitary adenoma (transfrontal operation and uniform medium voltage roentgen technique) Occurrence of insufficiency of gonades thyroid gland and adrenal cortex before and after treatment*

insufficiencies after treatment was the same among these 38 patients as among all 65 of the treatment group in whom the total target gland status could be judged only after treatment

Fig 7 shows the incidence of insufficiency of the respective target glands in the 38 patients before and after treatment It is apparent from the figure that gonadal insufficiency was commonest and that adrenocortical insufficiency was somewhat more common than hypothyroidism both before and after treatment. In 3 patients who had insufficiency of a single target gland (Table 13) the function of the gland became normal after treatment. On the other hand insufficiency of the gonads thyroid and

Table 13 — *Extension of target gland insufficiencies in 38 patients with chromophobe pituitary adenoma before and after treatment with transfrontal operation and uniform medium voltage radiation*
O = no target gland insufficiency, G = gonadal insufficiency,
T = thyroidal insufficiency, A = adrenocortical insufficiency

Before treatment: Target gland insufficiencies		After treatment: O	G	T	A	GT	GA	TA	GTA
	Number of patients	10	7	2	1	—	5	—	13
O	11	8		1					2
G	10	1	6				2		1
T	1			1					
A	3	1			1				1
GT	1		1						
GA	5						3		2
TA	2								2
GTA	5								5

of the 69 patients treated with *transfrontal operation and uniform medium voltage roentgen technique* Comparison was possible in only 10 of the patients in the other treatment groups

Of the above 38 patients, the endocrine status before treatment was intact in 11 Of these, the function remained intact in 8 after treatment, and in 3 patients *insufficiency of one or more target* glands was diagnosed (Table 13) Twenty-two patients showed evidence of insufficiency of one or two target glands before treatment After treatment the status was unchanged in 11 of these 22 cases (distributed along the diagonal in the table) while improvement was noted in 3 and new or additional target gland insufficiencies supervened in 8 (to the left respectively to the right of diagonal) In 5 patients all 3 target glands were insufficient both before and after treatment

An improvement of pituitary function after tumour treatment, as reflected in the target gland status, was thus observed in 3 cases In 11 cases a further impairment of the pituitary function was indicated by the supervention of additional target gland insufficiencies It should be mentioned that insufficiency of the thyroid gland and of adrenal cortex without coexisting gonadal insufficiency was noted in 5 men (Nos 89, 94, 100, 124 and 130) before and in 2 (Nos 93 and 124) after treatment, while 1 woman (No 76) had hypothyroidism both before and after treatment and a FSH of <40 MUU indicating that the production of gonadotrophins was intact It is also clear from Table 12 that insufficiency of 2 or 3 target gland functions was observed in 13 (one third) of these 38 patients before treatment and in 18 or one half of them after treatment The distribution of the target gland

judged thyroid function solely from the level of the basal metabolic rate

Data in the literature on adrenocortical function in patients with chromophobe pituitary adenoma are still more difficult to evaluate. Older investigations date back to the time when the function tests used were unreliable (NURNBERGER & KOREY 1953). Later studies often rely on the results of only single clinical signs or on the results of single functional tests which will not allow a firm diagnosis of adrenocortical insufficiency (MOGENSEN 1957, RUHSTRAT 1960, FISHER 1963).

In RUHSTRAT's series consisting of 47 patients who had been operated upon determination were made of the urinary excretion of 17 OHCS and intravenous ACTH test was performed in 15 cases. On the basis of these examinations 60 % of the patients were thought to have adrenocortical insufficiency. In the present group of patients treated with surgery and radiation the figure was 50 %.

The results of the present investigation show that the method of treatment used (transfrontal operation and roentgen treatment) has only a relatively slight effect on the pituitary function as judged from the target gland status.

In contrast to what is seen after therapeutic hypophysectomy, the insufficiency of the pituitary function due to chromophobe adenoma is most frequently relative, a fact which contributes to the complexity of the endocrine status of these patients and sometimes makes it difficult to interpret the endocrinological picture. It has long been assumed that the functions of the pituitary are involved in a certain chronological order: first the gonadotrophic, then the thyrotrophic and lastly the adrenocortitrophic function. But in the present series adrenocortical insufficiency in most cases appeared before thyroid insufficiency. This was also found by OBERDISSE (1957), MOGENSEN (1957) and ROSS (1961).

In the present investigation it was not possible to evaluate to what extent insufficient production of somatotrophic hormone influenced the endocrine status of these patients. The author feels however that the clinical picture of chromophobe pituitary adenoma is often largely decided by deficiency of somatotrophic hormone.

The effect of the target gland insufficiencies on the late results of treatment will be discussed in Chapter VII.

adrenal cortex supervened in 5, 7 and 5 cases respectively, *i e* an impairment of target gland functions in about 15 % after the treatment

DISCUSSION

The total target gland status before *treatment has apparently* been reported in only one series of patients with chromophobe pituitary adenoma (OBERDISSE 1957) *The distribution of single* or multiple target gland insufficiencies was largely the same as in the present series Normal gonadal function but insufficiency of the thyroid and/or *adrenal cortex* was possibly *slightly* more common in OBERDISSE's patients (about one fourth) than in the present series (about one sixth) OBERDISSE stressed that adrenocortical insufficiency may appear alone, a phenomenon also noted in the present investigation It should be observed that OBERDISSE did not *describe the criteria according to which he* judged the patients endocrine status

No attempts have heretofore been made to assess the effect of treatment of the tumour on the total target gland *status The results described here suggest* that in patients with insufficiency of only one target gland function, this may become normal though in most case it remains unchanged On the other hand, *the function of the pituitary is impaired* more by operation and roentgen treatment in patients with evidence of fairly marked involvement of the target gland status already before treatment

The *incidence of target* gland insufficiencies varies from series to series of patients with chromophobe pituitary adenoma This is probably ascribable to differences in the endocrinological evaluation Amenorrhoea was thus found by YOUNGHUSBAND ET AL (1952) and JEFFERSON (1957) in 50 % of the female patients This low *figure can probably* be explained by the fact that the series published by these authors included women in post-menopausal age MOGENSEN (1957), whose series obviously *included only younger women*, reported a frequency of 96 % This figure agrees better with the incidence found in the present patients, where amenorrhoea due to pituitary adenoma occurred in 85 % *of the women in* pre-menopausal age

NURNBERGER & KOREY (1953) judged gonadal function in men according to roughly the same principles as those used here In their series, as is in the present material, *half of the* patients showed evidence of gonadal insufficiency before treatment, while MOGENSEN found 25 % *of the men in his series to be important* After operative treatment MOGENSEN and FISCHER (1963) gave a frequency of male gonadal insufficiency about 70 %, but the data published by these authors do *not permit a definite opinion regarding* the real incidence of gonadal insufficiency in the males

Also in the evaluation of thyroid function NURNBERG & KOREY used largely the same criteria as those applied in the present investigation They found hypothyroidism *in one fourth of their* patients before treatment, *i e* the same incidence as in the present series The frequencies given by MOGENSEN and by FISCHER do not lend themselves to comparison here *because these authors*

judged thyroid function solely from the level of the basal metabolic rate

Data in the literature on adrenocortical function in patients with chromophobe pituitary adenoma are still more difficult to evaluate. Older investigations date back to the time when the function tests used were unreliable (NURNBERGER & KORFF 1953). Later studies often rely on the results of only single clinical signs or on the results of single functional tests which will not allow a firm diagnosis of adrenocortical insufficiency (MOGENSEN 1957, RUISTRAT 1960, FISHER 1963).

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The effect of the target gland insufficiencies on the late results of treatment will be discussed in Chapter VII.

CHAPTER VII
RESULTS OF TREATMENT

As pointed out in the introduction, opinions differ on the principles of treatment of chromophobe pituitary adenoma Thus, some authors advocate operation only, some radiation treatment only In most quarters combined treatment with surgery and radiation is the rule

In the present series most of the patients were subjected to transfrontal operation followed by roentgen treatment A few cases in which this principle of treatment was modified are accounted for in Table 4

The results obtained in the various groups of treatment are described below with reference to operative mortality, incidence of recurrences, duration of survival and of follow-up The results of treatment were also judged by the patient's working capacity, which depends on his visual capacity and endocrine status after treatment of the tumour A question that will be dwelt upon in this chapter is to what extent adequate hormonal replacement in endocrine insufficiency can improve or restore the working capacity of the patients

OPERATIVE MORTALITY, RECURRENCES, DURATION OF SURVIVAL AND FOLLOW-UP

The operative mortality was calculated on the basis of the number of patients who had died during or soon after the operation In the calculation those patients were also included in whom disturbances of the cerebral circulation occurred after operation and fairly soon resulted in death

When surgery and/or radiation treatment produced only a temporary effect (less than 1 year) on the clinical signs of tumour growth, the results of treatment were classified as uncontrolled growth in accordance with SHELINE, BOLDREY & PHILLIPS (*1964*) *Recurrences* were said to be present when clinical signs of expansion of the adenoma appeared after a free interval of at least 1 year

In the discussion of the operative mortality and duration of survival the size of the adenoma must also be considered An adenoma was said to be very large when described by the surgeon as the size of a golf ball or of a plum or still larger The growth of these adenomas is often asymmetric and

therefore the operative findings often differ from their encephalographic appearance

In the discussion of the results of treatment the cases will be described groupwise according to type of treatment in the same way as in the discussion of the visual disturbances and endocrine disorders Interest will also here be focused mainly on the largest group Data about the treatment given in the individual cases are found in Table 16, while the duration of survival and of follow up are given in Table 15 in the Appendix

A COMBINED TREATMENT (OPERATION AND ROENTGEN TREATMENT)

1 TRANSFRONTAL APPROACH AND RADIATION WITH UNIFORM MEDIUM VOLTAGE TECHNIQUE —The largest group consisted of 78 patients Postoperative roentgen treatment was intended or given by the technique used since 1946

At operation the adenoma was described as large in 26 of the 78 patients and as moderately large, *i e* about the size of a walnut in the remaining 52

In 9 patients (Nos 37 40 85, 87 125, 126, 127 128 and 131) the operation was soon followed by complications leading to a fatal outcome and thus preventing the intended roentgen treatment Two patients (Nos 126 and 131) with signs of increased intracranial pressure at the time of operation did not awaken after the operation In 1 case (No 87) operation was followed by epilepsy which could not be controlled In the remaining 6 patients haemorrhages and disturbances of the cerebral circulation occurred with ramollitio and a fatal outcome after a varying long period

Of the 9 patients who died at operation, 6 (Nos 37, 40, 85, 87, 126 and 131) had according to the operators reports, very large adenomas while in the remaining 3 the tumours were of moderate size

In recent years cortisone has been used routinely in association with operation of patients with cromophobe pituitary adenoma All the 5 patients who died at operation in 1959 and 1960 had received cortisone

In the surviving 69 patients in this group the roentgen treatment intended could be carried through. The late results of treatment in these 69 patients is seen from fig 8

Uncontrolled growth of the adenoma was observed in 2 patients (Nos 32 and 74) In both of them the adenomas were large and firm, so that only a relatively small portion of them could be removed Before the operation the adenoma in No 74 extended 55 mm above the entrance of the sella, as seen in the encephalogram. The size of the adenoma could not be estimated from the pre treatment encephalogram of patient No 32

Clinical recurrences were noted in 2 patients (Nos 56 and 92) 11 respectively 6 years after treatment. In both cases the primary adenoma was of moderate size In patient No 92 however, the tumour had a firm consistency and therefore only a small portion of it was removed In patient No 56 the major part of the tumour was removed After the first

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The cause of death in 1 patient (No 50) was according to the case records most likely severe hypopituitarism with unsubstituted adrenocortical insufficiency He died at home in 1956 7 years after the treatment He was then 72 years old One patient (No 81) died in 1958 at a department of surgery in a sudden shock after one week s observation because of obscure fever Judging from her record she might have had an acute adenocortical crisis Necropsy failed to explain the cause of death

The remaining 8 patients died from incidental diseases The causes of death were cerebral haemorrhage (Nos 45 49 and 83) gastric cancer (No 46) myocardial infarction (Nos 51 and 76) bronchopneumonia and pulmonary embolism (No 59) and epipharyngeal cancer (No 78) These 8 pati nts had been in hospital just before or at the time of death and the cause of death may be regarded as certain During their last spell in hospital these patients had shown no clinical evidence of recurrence Three of these 8 patients were examined post mortem Two (Nos 51 and 59) were found to have chromophobe pituitary adenoma the size of a pea while the third (No 46) showed only a very small residual pituitary in the sella turcica

At the end of 1965 fifty seven patients in this group were still living including the 2 patients (Nos 56 and 92) success fully treated for a recurrence The duration of follow up of 55 patients without clinical signs of recurrence was on the average 11 5 years (5 19 years) including 37 patients (67 %) who had been followed up for at least 10 years The duration of follow up of all 69 patients was on the average 10 5 years (3 19 years) The duration of survival and follow up is given in Fig 15

Fig 3 (page 30) gives the tumour doses used In this fractionation diagram the 2 patients (Nos 52 and 74) with uncontrolled growth of tumour and the 2 patients (Nos 56 and 92) with recurrence are indicated by solid squares and circles It is clear from the diagram that the 2 last mentioned patients were given a relatively small cumulative dose

2) TRANSFRONTAL APPROACH AND IRRADIATION WITH OLD TECHNIQUE —This group consisted of 15 patients One of them (No 22) however died at operation He had a very large adenoma All of the other 14 patients received post operative radiation

Recurrences appeared in 7 patients (Nos 14 18 26 27 29 30 and 31), on the average 11 years (4—25 years) after treatment Two of them (Nos 26 and 27) died from a large recurrent adenoma which was judged as inaccessible to treatment Two patients (Nos 30 and 31) also with large recurrent adenomas, received a further radiation course but died 1 year after this treatment One patient (No 18) who was operated upon and given roentgen treatment because of a very large recurrent adenoma soon developed clinical signs of continued growth of the adenoma and died after 5 years The remaining 2 patients (Nos 14 and 29) were still living at the end of 1965 after successful treatment of recurrences Patient No 14 was re operated upon for a fairly large recurrence after 25 years and operated upon again after a further 5 years—he was then 77 years of age—for a second moderately large recurrence Large roentgen doses had been given after the primary operation No roentgen treatment was given after the re operations At the end of 1965, barely 2 years after the last operation the patient had satisfactory visual capacity

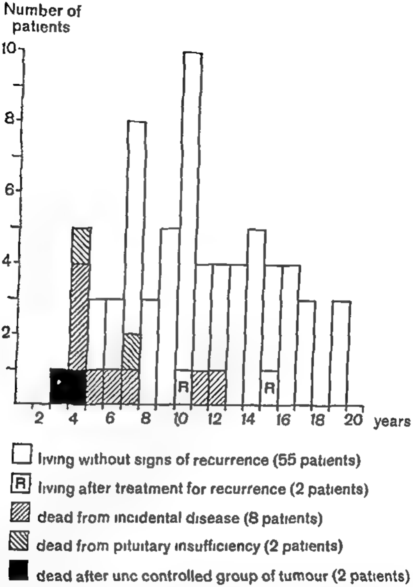

Figure 8 *Interval between treatment and end of 1965 or until death in 69 patients uniformly treated with transfrontal operation and medium voltage roentgen technique used since 1946*

operation the patients were given roentgen treatment with a total tumour dose that was relatively small, compared with that given in the remaining cases (see *Fig 3, page 30*) *Patient No 56* received *1,600 r/15* days and *patient* No 92 received 2,900 r/26 days After re-operation both patients received a supplementary radiation course adjusted according to that given after the primary operation No further clinical signs of recurrence were seen at the last examination of these 2 patients in 1965, *i e* 4 years after the re-operation

At the time of the re-examination 10 patients had died without clinical signs of recurrence These 10 patients had been followed up for, on the average 6 5 years (4—12 years)

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and no certain target gland insufficiency Patient 29 was re-operated upon for a recurrence after 4 years and was then given post-operative roentgen treatment with the newer technique When last seen at the end of 1965, 16 years after the re-operation, she had no signs of a recurrence

In the remaining 7 patients in this group no clinical signs of a recurrence of the adenoma were observed during follow-up Three of them (Nos 11, 12, and 24) died at the age of 75 from cerebral haemorrhage and cardiac incompensation, 13—23 years after the treatment At the end of 1965 four patients (Nos 23, 25, 38 and 39) were still living, 18—25 years after the treatment

3) TRANSFRONTAL APPROACH (BIOPSY ONLY) AND IRRADIATION —This group consisted of 5 patients Recurrences developed in 2 of them (Nos 62 and 77) Patient 77 died, 8 years after treatment, of a large subfrontal recurrence with increased intracranial pressure and symptoms of compression of the brain stem Histological examination after autopsy showed no changes ascribable to roentgen treatment In patient No 62 clinical signs of recurrence appeared 1 year after biopsy and roentgen treatment with a special stereotaxic technique (see Chapter III) No further roentgen treatment was given after the re-operation The patient was still living at the end of 1965 without signs of recurrence, 12 years after primary treatment

One patient (No 68) died in 1961 with the clinical picture of adrenocortical failure (see page 79) 9 years after treatment

Two patients (Nos 71 and 96) belonging to this group were living in 1965 without clinical signs of a recurrence Follow-up was 11 and 8 years respectively

4) TRANSSPHENOIDAL APPROACH AND RADIATION —This group consisted of 2 patients (Nos 117 and 119) One (No 117) of them developed uncinate fits after barely one year Already at the first operation there was a very large adenoma with a wide extension into the right temporal fossa, which had not been observed at the preoperative examination or at the transsphenoidal operation At the transfrontal re-operation the temporal part of the tumour had expanded further and only a relatively small portion of the adenoma was removed at the operation, after which the patient was given a further radiation course The patient was able to continue his work for almost 5 years, but in 1965 he deteriorated with signs of further growth of the adenoma

The second patient (No 119) had a moderately large adenoma Examination at the end of 1965, 7 years after treatment, showed no signs of recurrence

B SURGICAL TREATMENT ONLY

This group consisted of 7 patients who for various reasons did not receive postoperative roentgen treatment (see Chapter III) In 2 of them (Nos 47 and 65) the adenoma was very large and only part of it could be removed

The tumour recurred in 5 patients, in 4 of them (Nos 17, 36, 47 and 65) 1 5—4 years and in 1 (No 73) 13 years

after the operation Patient No 36 died at the re operation In patient No 47, a very debilitated woman with a large adenoma, all treatment was considered meaningless Patient No 65 was given roentgen treatment after re operation for a very large adenoma He died 6 years later and judging from his records, from adrenocortical insufficiency Patient No 17 was re operated upon 1 5 years later and was then given postoperative roentgen treatment He died 21 years later from cerebral haemorrhage In patient No 73 a large recurrence was diagnosed in the autumn of 1965 He was re-operated upon and afterwards given roentgen treatment

Two patients (Nos 16 and 90) showed no signs of recurrence last seen at the end of 1965 Follow up 30 and 10 years The prevalence of rather early relapses in this group is noteworthy

C ROENTGEN TREATMENT ONLY

1) PATIENTS WITH SIGNS OF OPTIC NERVE COMPRESSION —The group consisted of 19 patients The reasons why these patients were not operated upon are accounted for in Chapter III

In 10 patients (Nos 3 5 6 7, 9 22 41 55 104 and 109) treatment had produced only a slight temporary effect on the growth of the tumour and the patients died within 1—5 years from their tumour According to the case records, all 10 patients were in a very poor general condition In 9 of them the records also suggested that the tumours were large and that many of the patients had also had pronounced adrenocortical insufficiency

In 9 patients treatment had produced a good primary effect Recurrences had appeared in only 3 of them (Nos 1, 2 and 20) after 12, 4 and 9 years After a further course of roentgen treatment or operation (No 20) these 3 patients lived without signs of a recurrence for 5—13 years after the re-treatment In 6 of the above 9 patients no signs of recurrence were seen during follow up Five of them had died before the re-examination, on the average 10 years (1—25 years) after treatment The causes of death in these cases were pituitary insufficiency (No 4), cerebral haemorrhage (Nos 8 and 15), metastasising cancer (No 13) and thrombocytopenia (No 82) The mean age of these 5 patients at death was 71 years (53—80 years) At the end of 1965 1 patient (No 10) in this group was living, 36 years after treatment

2) PATIENTS WITHOUT SIGNS OF OPTIC NERVE COMPRESSION —This group consisted of 5 patients in whom operation was not considered indicated (see Chapter III)

Ophthalmoneurological signs of suprasellar expansion supervened after 2 and 4 years respectively in 2 patients (Nos 19 and 28) who had been treated with the older roentgen technique At the time of the operation both had very large adenomas which could only be incompletely removed Further roentgen treatment was not given The operation resulted in temporary clinical improvement, and the patients died 6 and 8 years later from their disease

In the remaining 3 patients in this group (Nos 99, 102 and 115) there were no clinical signs of extrasellar expansion

of the adenoma up to the end of 1965 Follow-up was 7—18 years These patients had been treated by the newer roentgen technique

OPERATIVE MORTALITY RATE

119 operations, including 11 re-operations, were performed Of these patients, 11 died from complications at operation, one of them at the re-operation The overall operative mortality was thus 9 2 % In the larger group of 78 patients, where postoperative roentgen treatment had been intended with the uniform medium voltage technique, 80 operations were performed, including 2 re-operations Nine (11 3 %) operative deaths occurred in this group Of these 6 (23 %) occurred among the 26 patients in the group with very large adenomas, while 3 (5 8 %) occurred among the remaining 52 patients with relatively small or moderately large adenomas

THE WORKING CAPACITY IN THE GROUP OF PATIENTS UNIFORMLY TREATED WITH SURGERY AND RADIATION

Below an account is given of the patients' working capacity after treatment and of factors influencing working capacity As before, interest is focused mainly on the large group of 69 patients The working capacity of the remaining patients will not be discussed in detail

It was possible to estimate the working capacity of all 69 patients in the large group after treatment Of these patients, 9 had died The remaining 60 were interviewed by the author personally at the re-examination

The working capacity of the 9 who had died was estimated from the detailed data in the clinical records

At the time of the re-examination 16 patients were living with known thyroid and/or adrenocortical insufficiency without substitution therapy In 15 of these patients replacement therapy was then started and continued The working capacity of these patients was judged after substitution treatment had achieved its full effect

Of the 69 patients, 56 were in working age, *i e* below 67 years Working capacity was unimpaired in 40 (58 %) In 7 there was a slight to moderate reduction of working capacity All together 47 (68 %) patients were still at work or their activity as pensioners was considered satisfactory (table 14)

More or less severe disability was noted in 22 (32 %) patients, including 13 who could take care of themselves with only little help, while 9, including 5 living at departments for chronic diseases, were completely dependent on others' help

CAUSES OF IMPAIRED WORKING CAPACITY

Reduced visual capacity was the main cause of reduced working capacity in 12 (17 %) patients A more detailed report is given in Chapter IV Despite marked impairment of vision 2 (Nos 63 and 89) of these patients could still manage their occupation, practically unhindered, and 1 (No 120) was obliged to change her occupation to one not requiring good vision Nine patients (Nos 35, 42, 60, 67, 69, 76, 81, 95 and 100) were completely disabled by impair-

Table 14 *Working capacity of 69 patients uniformly treated with operation and radiation*

Working capacity	Number of patients	Normal working capacity	Working capacity reduced by visual reduction only	visual reduction + pituitary insuff	pituitary insuff only	other causes
		40	12	2	7	8
Full capacity for former occupation	40	40				
Reduced capacity but still in former occupation	5		2		3	
Reduced capacity changed occupation	2		1		1	
No working capacity but can manage self-care	13		6		2	5
No working capacity cannot manage self-care	9		3	2	1	3

ment of vision In 3 of them (Nos 42 67 and 100) working capacity was also slightly reduced by endocrine insufficiency despite substitution therapy Six of the 9 disabled patients could still take care of themselves but 3 (Nos 60, 81 and 100) were largely dependent on help because of their loss of vision

Visual reduction and pituitary insufficiency togheter reduced the working capacity to largely the same extent in 2 of the patients (Nos 50 and 74) Both had died before the re examination and neither had received substitution therapy They had been largely dependent on help from their entourage

Pituitary insufficiency and then above all pronounced adrenocortical insufficiency was apparently the predominent cause of more or less marked reduction of working capacity in 7 (10 %) patients Slight to moderate reduction was reported by 4 patients who were receiving adequate substitution therapy Three of them (Nos 44 103 and 123) could however continue their previous occupation while 1 (No 101), a miller had changed his occupation and had a lighter job Three patients (Nos 32 46 and 75) were completely disabled by their endocrine insufficiency Two of them (Nos 46 and 75) had adequate substitution therapy but nevertheless complained of fatigue and thought they could not continue their usual occupation (antiquarian respectively engineer) Finally 1 patient (No 32) who died in 1950 had been unable to manage without help He had never received adequate substitution therapy

Other causes of reduced capacity *i e* other than impairment of vision and pituitary insufficiency, were noted in 8 (12 %) patients, *including 3 (Nos 59 72* and 88) who were being cared for at departments for chronic diseases Two patients (Nos 66 and 88) were disabled by sequelae after cerebral injury in association with operation. Pronounced senility apparently unrelated to endocrine

insufficiency, was noted in 3 patients (Nos 49, 59 and 72) One patient (No 78) suffered from sequelae after cerebral thrombosis Finally, 2 patients (Nos 70 and 121) had disabling psychoneurosis Repeated examinations during follow-up of these patients gave no reasonable somatic cause of the inability to work

In this connection it should be mentioned that *epileptic seizures*, usually sporadic, occurred in 9 patients who had been operated upon and received post-operative roentgen treatment In none of these patients was working capacity more than occasionally reduced by these attacks Four (Nos 56, 88, 92 and 93) of them required permanent treatment with antiepileptics, which had a good effect on the frequency of their attacks

IMPORTANCE OF HORMONAL REPACEMENT IN PATIENTS WITH ENDOCRINE INSUFFICIENCY

The importance of adequate substitution therapy in patients with known thyroid and/or adrenocortical insufficiency is elucidated below The experience gained in this respect is based on 45 patients from the entire series, irrespective of type of tumour treatment given In 10 of them substitution therapy had evidently been indicated but not given, or had been stopped after a short period In 35 patients substitution therapy apparently was adequate Eleven of the 45 patients were dead, while 34 were living and thus included in the present re-examination In the 11 patients who had died the course of the disease could be evaluated from the patients detailed hospital records including laboratory data In the evaluation of the working capacity of these cases, in this connection, only reduction of working capacity due to endocrine insufficiency was considered

The analysis of the working capacity of the above 45 patients will be preceded by a description of the *principles of hormonal replacement* used

In those cases where adrenocortical insufficiency could be demonstrated hormonal replacement was always started with cortisone usually 25 mg daily per os This basal dose was increased in patients doing heavy work In the event of stress situations such as severe infections with impairment of their general condition the patients were requested to contact their physician who had been informed of the patient s condition At later follow up patients in whom hypothyroidism was diagnosed were given substitution for this The dose of the thyroid preparation was adjusted individually but was usually 120—240 mg desiccated thyroid or 0 1—0 2 mg synthetic laevothyroxin a day The patients were seen at regular intervals and the doses of cortisone and thyroid preparation were selected according to the patients condition Women with gonadal insufficiency were not given hormonal replacement for this Males with hypogonadism were sometimes given adrogenic hormone formerly by implantation of pellets but in recent years mostly by intramuscular injection of long acting preparations

No hormonal replacement given Ten patients had either not received substitution therapy (Nos 19, 22, 32, 41, 50, 65 and 103) or such treatment had been stopped after a short time (Nos 68, 71 and 73) All of them had insufficiency of all 3 target glands Nine of these patients were completely disabled after treatment of the tumour Five of them were admitted to department for chronic diseases and in 8 death was due with

certainty to severe pituitary insufficiency The mean duration of survival of these 8 patients was 5 years (1—9 years) and the average age at death was 57 years (31—75 years)

Two of these 10 patients were still living at the end of 1965 One of them (No 71) was then 60 years old He had been operated upon 11 years previously and he had for many years been completely disabled by the marked impairment of visual capacity and by extreme fatigue and sluggishness At the re examination substitution therapy was started, but the patient took the preparation for only a short time The working capacity of the other patient, a 62-year old clerk (No 103), was moderately reduced In the 9 years after treatment, however he had still been able to carry on with his work At the re-examination he was offered replacement therapy but refused

The course of the disease in the patients who did not receive replacement therapy is examplified below by 2 illustrative cases

Patient No 32 A 59-year old elementary school teacher had for 5 years attended a department of internal medicine because of increasing fatigue and intol rance to cold He was admitted several times for investigation and hypothyroidism and anaemia were diagnosed The patient was treated with thyroid liver and iron preparations as well as with tonics all without effect His vision gradually became impaired and this led to the diagnosis of pituitary adenoma He was operated upon in 1946 and afterwards received roentgen treatment Vision improved considerably and for a short time he was able to return to his work He became increasingly tired and sluggish and periodically he had fever of unknown cause somnolence nausea and occasionally painful tonic cramps of the muscles of the limbs with contractures The patient died 63 yers old in 1950 4 years after the operation without ever having received adequate substitution therapy

Patient No 68 A 45 year old builder was treated with surgery and radiation in 1952 Three years later insufficiency of all 3 target glands was diagnosed at the department of medicine Lund and replacement therapy was instituted The patient was seen at regular intervals at his local hospital but after 3 years he ceased taking the preparation During the following 2 years he became increasingly tired and sluggish and he could no longer manage his work In association with an unexpectedly long convalescence after a fracture of a rib and haemothorax the patient was examined at the department of medicine of his local hospital. Because of his psychic deterioration in 1960 he was referred to a mental hospital for further care and he died there in 1961 at the age of 54 surely because of severe hypopituitarism with advanced adrenocortical insufficiency

Hormonal replacement given In 35 patients adequate substitution therapy had been given for insufficiency of both the thyroid and of the adrenocortex in 23, and for hypothyroidism or adrenocortical insufficiency alone in 6 of each group Hormonal replacement was started in 11 patients soon after the beginning of treatment of the tumour, and in 9 patients later In 15 patients it was started as a result of investigation at the present re-examination

In 26 patients working capacity was unreduced or recovered after hormonal replacement Despite this treatment 7 patients (Nos 24 42 44 67 100 101 and 123) still complained of moderatly reduced working capacity and 2 (Nos 46 and 75) thought that they were still disabled by severe tiredness

All the patients responded more or less well to hormonal replacement The effect

of the treatment was marked in 27 patients, in 12 of them the working capacity had previously been moderately reduced, and 15 had been completely disabled In 3 patients (Nos 24, 42 and 67) the effect of hormonal replacement was dramatic

The effect of hormonal replacement is elucidated below by 3 illustrative case histories

Patient No 24 A 54 year old woman was operated upon in 1941 because of a moderately large pituitary adenoma and was afterwards given roentgen treatment After treatment her visual field and visual acuity were slightly reduced No investigation of her endocrine status was made in association with treatment of the tumour or during follow up She continued her work as a clerk until the age of 65 From about 7 years she became more and more sluggish and had repeated attacks of bronchopneumonia Examination at the local hospital revealed signs suggesting adrenocortical insufficiency and for a while she was given prednisolone The patient was transferred to a department for chronic diseases where she was treated with bed rest and no hormonal replacement She was very sluggish and could not manage her personal hygiene At the present re examination the patient was then 75 the woman was found to have severe adrenocortical insufficiency and hypothyroidism Treatment with cortisone was started and 1 month later the patient could be discharged from the department for chronic diseases and could manage her own home with only little help with the heavier chares Later on treatment with thyroid substitution was also started

Patient No 67 A 53 year old housewife was operated upon and given roentgen treatment in 1952 because of a moderately large adenoma After the operation she was blind on one side and on the other side vision was limited to the upper nasal quadrant At investigation of her endocrine status in 1954 adrenocortical insufficiency and hypothyroidism were suspected Hormonal replacement therapy was started and should have been controlled at the local department of medicine After a while however the hormonal replacement was stopped She then became more and more tired and sluggish she could not look after herself and remained in bed the major part of the day at home Because of her condition she was again admitted to hospital The fatigue was ascribed to anaemia and she was given iron preparations and tonics without effect At the re examination in 1961 the patient showed all signs of grave adrenocortical insufficiency Thyroid function was normal She was given cortisone which had a dramatic effect on her condition At later follow up she was in an excellent condition

Patient No 122 A 48 year old painter and decorator had for 8 years suffered from increasing fatigue impotency and intolerance to cold He had sought several physicians for these symptoms and had been treated with iron preparations and tonics without success From the age of 46 he had been unable to work In 1959 he attended the department of medicine of his local hospital where chromophobe pituitary adenoma with insufficiency of all target glands was diagnosed His vision was only slightly impaired which had not bothered him much Hormonal replacement was started and later the patient was operated upon because of a moderately large adenoma after which roentgen treatment was given Half a year later the patient was again able to return to his work and in 1965 he was then 54 he was still at work

DISCUSSION

In Chapter III an account is given of the reasons for deviation from the routine treatment, transfrontal approach and medium voltage roentgen treatment, in the management of patients in this series, and the material is divided into different treatment groups Many of these groups consisted of few patients, and the diseases were of widely different degrees of severity It is therefore not possible to estimate the relative

value of the individual methods of treatment from the results obtained in the different groups in this series

In patients with signs of compression of the optic chiasma and nerves operation was considered indicated irrespective of the size of the adenoma The only exceptions were those patients in whom operation was contraindicated mainly by their extremely poor general condition The series thus included cases with tumours of widely varying size and spread

It is well known among neurosurgeons that the risks of operation are much greater if the adenoma is large with substantial suprasellar extension than if the tumour is small This is because the large tumours often cause considerable compression and distorsion of the brain stem and advanced pituitary insufficiency, *i e* factors which increase the risk of surgery

JEFFERSON (1940) reported an operative mortality of 33 % in patients with large adenomas Corresponding frequencies between 30 and 35 % have since been reported by BAKAY (1950), HORRAX ET AL. (1952) and HEIMBACH (1959) Even CUSHING reported a high mortality and therefore according to WHITE (1955) he stopped operating on patients with large adenomas This attitude was later adopted in HEIMBACH's (1959) series This reduced the operative mortality to less than 5 %

A corresponding division of the large group of 78 cases in the present series showed the same tendency with a mortality of 23 % for large adenomas and 5 8 % for small ones Of the 20 patients who had large adenomas and who survived the operation, treatment had a good effect in all except 2, in whom the effect was only temporary

In the discussion of indications for operation of large pituitary adenomas the results obtainable by roentgen treatment alone must also be considered The present series of cases with large adenomas treated with radiation alone was small and very selected and therefore allows of no conclusions According to DECKER & LAUTER (1960) and POPPEN (1963) the results of treatment of large adenomas with radiation alone were less favourable It would therefore appear justified to maintain the fairly active attitude which characterises the surgical treatment of large adenomas in the present series (LUNDBERG 1966)

The overall mortality was 9 3 % in the present series of 119 transfrontal operations on 109 patients with 11 operative deaths, one of them at re-operation This operative mortality was of the same order as that, 8—15 %, reported by several other workers in the field (BAKAY 1950 JONNIS OBERDISSE & WEBER 1952, MOGENSEN 1957, POPPEN 1963 and SHELINE, BOLDREY & PHILLIPS 1964) Perusal of the literature revealed only 3 series of patients treated with transfrontal operation and radiation and reported with sufficient data to allow comparison with the present 69 patients These series were published by HENDERSON (1939) 31 patients BAKAY (1950), 130 patients, and SHELINE, BOLDREY & PHILLIPS (1964) 34 patients The frequency of recurrences in the series of HENDERSON was 13 %, in that of

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was below the lowest level for cerebral necrosis observed after fractionated irradiation of adult brains in a clinical material by LINDGREN (1958). He, however, stressed that the slope found in his study must be regarded as tentative and that necrosis may appear even after smaller doses. Severe radiation reactions are presumably very rare and possibly reflect the individually varying tolerance to radiation. No other observations suggesting impairment of function in the hypothalamus or pituitary by radiation have been published.

In none of the cases in the present series was treatment followed by a permanent diabetes insipidus. The thyroidal 24 hour radio-iodine uptake had been examined in 57 of the present patients. In all except 2 the uptake was as high as 20 to 50 %, also in patients who had clinically certain hypothyroidism. This may be taken as a sign of preserved thyrotropin production (LI ET AL. 1955, SKANSE 1961) and argues against serious injury to the hypothalamus-pituitary function by the treatment given.

It was shown in Chapter VI that the symptoms of pituitary insufficiency increase after transfrontal operation and roentgen treatment. It is however not possible to decide whether it is the operation or roentgen treatment or if both are responsible for this increase. In MOGENSEN's (1957) series of 53 patients, 43 of whom were only operated upon, there was a fairly increase in the signs of target gland insufficiencies after treatment. There are no such investigations published of patients treated with radiation alone. Since hormonal replacement therapy is now available the risk of pituitary insufficiency is no longer any reason to refrain from post operative roentgen treatment, since this treatment as shown is of considerable importance in the prevention (or retardation) of recurrences.

In this chapter an attempt was made to judge the late results of treatment. The working capacity of the patients and their possibility to lead an ordinary life are largely dependent upon their vision and their endocrine status after treatment. Insufficiency of the target glands, particularly of the adrenal cortex and thyroid, impairs working capacity if adequate treatment is not given. In the present group of 69 patients treated with operation and radiation 40 (58 %) were able to carry on with their usual work, 7 (10 %) were slightly disabled and 22 (32 %) were completely disabled. Impairment of vision was responsible for reduction of working capacity in 12 (17 %) patients and insufficiency of the target organs in 7 (10 %). In all except 3 (all 3 disabled) of these 69 patients the working capacity was estimated after they had received adequate substitution therapy following a thorough investigation of their endocrine status. The findings showed that in hypothyroidism and adrenocortical insufficiency homonal replacement is necessary for maintenance or recovery of the working capacity of these patients.

Several of the present patients had severe endocrine insufficiency which had not been observed by their physicians. Despite an urgent need of hormonal

BARAY 10—15 %, and in the series of SHELINE, BOLDREY & PHILLIPS it was 21 %

All the patients in these 3 series had been followed up for at least 5 years During the first 5 years of follow-up 75—95 % of the recurrences occurred, including cases with uncontrolled growth of tumour

In the present group of 69 patients with a follow-up of 5—19 years (average 10 5 years) there were 2 cases with uncontrolled growth and 2 with recurrences, which gives a total frequency of 5 8 % This result was thus better than that achieved in the above-mentioned series, especially since the follow-up was much longer in the present series

In the series of HENDERSON and BARAY roentgen treatment was given with the older technique and with relatively low tumour doses In the series of SHELINE, BOLDREY & PHILLIPS (1964) a modern radiation technique was used, but with widely different tumour doses In the last mentioned series it was obvious that most of the recurrences occurred among those patients who had received *low tumour doses In the present series the patients were given relatively large tumour doses of 3,000—3,500 r in a fractionation time of 20—80 days Only 5 of the 69 patients received doses of less than 3 000 r* It should be observed that this group of 5 patients included the 2 who had recurrences This experience thus is the same as that in SHELINE, BOLDREY & PHILLIPS' (1964) series

HENDERSON (1939) found a transfrontal operation with postoperative roentgen treatment to produce better results than transfrontal operation alone MOGENSEN (1957) reported recurrences in 14 % of 43 patients, treated with transfrontal operation alone In the present series 7 patients were treated with operation alone and 5 of them had recurrences Observations made in the present series of patients operated upon with transfrontal approach thus suggests that postoperative radiation is of great importance and prevents or retards the development of recurrences Experience also suggests that this treatment should be given with tumour doses of about 4,000 r which is now the rule at most centres (HORRAX 1956, HEIMBACH 1959, DECKER & LAUTER 1960, RAY & PATTERSON 1962, POPPEN 1963, SHELINE, BOLDREY & PHILLIPS 1964)

Tonnis and co workers (TONNIS, OBERDISSE & WEBER 1952, MARGUTH 1959) and MOGENSEN (1957) claimed that roentgen treatment carries a risk of injury in the region of the pituitary and hypothalamus As far as is known, these authors published *no clinical observations in support of their view MOGENSEN's opinion is based on observations* made by ARNOLD (1954) in experiments *on monkeys* According to these experiments, the risk of injury to the paraventricular and supraoptic nuclei occurs on delivery of doses exceeding 3 000 r single dose Since then CROMPTON & LAYTON (1961) and ALMQUIST ET AL (1964) have reported detailed studies of individual patients with severe injury following radiation treatment The doses used by CROMPTON & LAYTON were above and that used by ALMQUIST ET AL

was below the lowest level for cerebral necrosis observed after fractionated irradiation of adult brains in a clinical material by LINDGREN (1958) He however, stressed that the slope found in his study must be regarded as tentative and that necrosis may appear even after smaller doses Severe radiation reactions are presumably very rare and possibly reflect the individually varying tolerance to radiation No other observations suggesting impairment of function in the hypothalamus or pituitary by radiation have been published

In none of the cases in the present series was treatment followed by a permanent diabetes insipidus The thyroidal 24 hour radio-iodine uptake had been examined in 57 of the present patients In all except 2 the uptake was as high as 20 to 50 % also in patients who had clinically certain hypothyroidism This may be taken as a sign of preserved thyrotropin production (LI ET AL 1955 SKANSE 1961) and argues against serious injury to the hypothalamus pituitary function by the treatment given

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In this chapter an attempt was made to judge the late results of treatment The working capacity of the patients and their possibility to lead an ordinary life are largely dependent upon their vision and their endocrine status after treatment Insufficiency of the target glands, particularly of the adrenal cortex and thyroid impairs working capacity, if adequate treatment is not given In the present group of 69 patients treated with operation and radiation, 40 (58 %) were able to carry on with their usual work, 7 (10 %) were slightly disabled and 22 (32 %) were completely disabled Impairment of vision was responsible for reduction of working capacity in 12 (17 %) patients and insufficiency of the target organs in 7 (10 %) In all except 3 (all 3 disabled) of these 69 patients the working capacity was estimated after they had received adequate substitution therapy following a thorough investigation of their endocrine status The findings showed that in hypothyroidism and adrenocortical insufficiency homonal replacement is necessary for maintenance or recovery of the working capacity of these patients

Several of the present patients had severe endocrine insufficiency which had not been observed by their physicians Despite an urgent need of hormonal

therapy these patients never received such treatment Many of them were severely disabled, some of them had been referred to a department for chronic diseases and several of them had died, obviously from pituitary insufficiency

If treatment is to be really successful, patients with chromophobe pituitary adenoma should be followed by regular examinations of their endocrine status by an internist interested in endocrinology This follow-up should be done in cooperation with an ophthalmo-neurologist and with those specialists responsible for the primary treatment of the tumour In view of the tendency of the tumour to recur even many years after primary treatment, it is desirable that the patient should be regularly examined during the rest of their lives It has often been stressed that the disease in these patients has often been misdiagnosed and treatment neglected A passage from KOEPFF & VIEILLARD (1954) still holds good "A missed or poor understanding of the physiology involved in a recognized case of moderate to severe hypopituitarism will undoubtedly result in early death On the other hand, the prompt institution of well-planned therapy will usually result in striking improvement and economic rehabilitation of a large percentage of these patients "

SUMMARY AND CONCLUSIONS

A clinical review is given of 131 patients with chromophobe pituitary adenoma treated at Lasarettet Lund, in the years 1921—1960 Of these cases, 100 were treated during the last 15 years of the period The diagnosis of chromophobe adenoma was made on clinical grounds All of the patients had an intrasellar tumour with or without suprasellar extension None of them showed signs of pituitary hyperfunction while several showed evidence of pituitary insufficiency In 111 cases the clinical diagnosis was confirmed at operation and by histological examination of the operative specimens

The series consisted of 53 women with a mean age of 46 years (range 17—70) and 78 males with a mean age of 49 years (range 14—74) All of the 80 patients still alive in 1960—1961 were re-examined by the author personally The patients were followed up until the end of 1965 when 75 were still living

The development of the clinical picture until the time of diagnosis was studied and described in detail The initial symptoms at onset were visual disorders in 42%, headache in 14% and symptoms of target gland insufficiency in 44% The corresponding figures at the time of the diagnosis were 90, 54 and 60% In the patients in whom the initial symptoms were visual disturbances the average interval between the onset and diagnosis of the disease was 3 years The corresponding interval for headache and pituitary insufficiency were 5 years and 7 years, respectively Various factors contributed to this delay When the onset of unilateral visual disturbance was gradual the patients often waited a long time before they sought medical advice When the onset was sudden or when the disturbance was bilateral advice was as a rule, sought without delay A fairly large number of the patients had for many years had more or less severe symptoms of pituitary insufficiency but did not consult a physician until a fairly acute supervention of visual disturbances In about 10% of the patients the diagnosis was delayed at least 2 years because of misinterpretation of the ophthalmological findings In roughly the same number of patients who had for several years sought advice for their symptoms of pituitary insufficiency the latter had also been misinterpreted

With the increasing improvement of

the standard of living and of education, patients with chromophobe adenoma will probably seek advice *earlier than those* in the present series If the diagnosis is not to be unnecessarily delayed the examiner should bear in mind the possibility of chromophobe adenoma in patients seeking advice because of such symptoms as amenorrhoea, impotence, headache, *fatigue and weakness, i e, all early* signs of the tumour

After surgical treatment became available in the 1930s all patients with signs of compression of the optic chiasma and nerves were operated upon by the transfrontal route and given postoperative radiation treatment *From 1946* postoperative treatment was given with a standardised medium voltage roentgen technique For several reasons the patients were assigned to different groups according to the treatment given The largest group consisted of 69 patients treated *with the transfrontal operation* and postoperative radiation in 1 or 2 series with a tumour dose of 3,000—4 500 r/20—80 days

The visual disturbances, radiologic changes and endocrine disorders before and after treatment are described An *analysis is given* of the results of treatment, of the operative mortality, recurrences, duration of survival and working capacity of the patients with special reference to the above mentioned group of 69 patients

Of this main group of 69 patients, treatment produced more or less marked and permanent improvement of the visual field defects in 40% In 15% the defects disappeared In 15% the visual field defects increased after treatment More or less pronounced improvement of *visual* acuity was noted in 53% Visual acuity improved considerably in 53%, in 20% it became normal and in 13% it became worse after treatment Since about one third of the 69 patients had very large adenomas the results of transfrontal operation and postoperative radiation must be regarded as having had a satisfactory effect on the intracranial pressure and on the optic chiasma and nerves It should be stressed that also in the group of patients treated with radiation only, the treatment often had a good and permanent effect on the patient's vision

Observations made in the present series showed that in the calculation of visual disability expressed in percent of normal visual acuity, 20—25% should be added for coexisting visual field defects, if any Severe, disabling impairment of *vision was noted after treatment in* 17% of the 69 patients The corresponding figures in series on record range from 25 to 36%

Check-examination of pre-treatment encephalograms available showed that in the majority of the patients (81%) the suprasellar part of the adenoma had a height of 15—30 mm The encephalograms usually gave satisfactory information on the size and extent of the tu*mours, but in a few cases the tumours* were asymmetric and then the encephalo gram did not show the true size of the growth The check-examination showed that air encephalography is indicated in all cases of *clinically suspected recur-*

rences since a recurrence is not always accompanied by the appearance of new skeletal lesions Post treatment encephalograms occasionally revealed atrophic changes of the tissue surrounding the basal cisterns and the anterior horn of the lateral ventricle on the operated side The significance of these changes is discussed

The effect of treatment on pituitary function as reflected in the function of the target glands (gonads, thyroid and adrenal cortex) was analysed especially in the aforementioned group of 69 patients treated in a uniform way Certain relevant diagnostic problems are discussed It was found that the pituitary insufficiency in patients with chromophobe adenoma is practically always relative Assessment of the function of the target glands is therefore often difficult In the present investigation target gland function was assessed on the basis of all available data on anamnestic symptoms bedside observations and laboratory tests In some cases the diagnosis was decided by tentative replacement therapy In most published series the diagnosis of target gland insufficiency was based on single data

In one group of patients treated with transfrontal operation and radiation there was evidence of gonadal insufficiency in 55% before and in 66% after treatment. Signs of hypothyroidism were seen in 24% and 39% and of adrenocortical insufficiency in 39% and 50% respectively Thus judging from the function of the target glands treatment produced only a moderate decrease of pituitary function

All together 119 transfrontal operations were performed on 109 patients with an operative mortality of 9.3% As expected, it was higher (23%) among patients with a very large adenoma and lower (5.8%) among patients with small to medium sized adenomas It would appear justified to operate also on patients with very large adenomas, since radiation alone will often have only a temporary effect in such cases

In the group of patients treated with operation and radiation, treatment produced only a temporary effect on the growth of the tumour (uncontrolled growth) In both cases the tumour was very large True recurrences after 6 and 11 years occurred in 2 patients who had received roentgen doses substantially smaller than the average dose used in that group In view of the long follow up period of 10.5 years (range 5—19 years) this result (total incidence of recurrences 5.8%) must be regarded as good In other published series where relatively small doses were used and where the follow up was much shorter the frequency of recurrences was 10—15% For comparison it might be mentioned that of 7 patients who were operated upon but did not receive post operative radiation as many as 5 developed recurrences In 1 group of 14 patients who were operated upon and given small roentgen doses recurrences developed in 7

It appears that postoperative radiation with adequate doses is necessary to prevent or delay recurrences of adenoma Observations made in the present series showed that even when adequate post

the standard of living and of education, patients with chromophobe adenoma will probably seek advice earlier than those in the present series If the diagnosis is not to be unnecessarily delayed the examiner should bear in mind the possibility of chromophobe adenoma in patients seeking advice because of such symptoms as amenorrhoea, impotence, headache, fatigue and weakness, *i e*, all early signs of the tumour

After surgical treatment became available in the 1930 s all patients with signs *of compression of the optic chiasma and* nerves were operated upon by the transfrontal route and given postoperative radiation treatment From 1946 post operative treatment was given with a standardised medium voltage roentgen technique For several reasons the patients were assigned to different groups according to the treatment given The largest group consisted of 69 patients treated with the transfrontal operation and postoperative radiation in 1 or 2 series with a tumour dose of 3,000—4 500 r/20—80 days

The *visual disturbances, radiologic* changes and endocrine disorders before and after *treatment are described An* analysis is given of the results of treatment, of the operative mortality, recurrences, duration of survival and working capacity of the patients with special reference to the above mentioned group of 69 patients

Of this main group of 69 patients, treatment produced more or less marked and permanent improvement of the visual field defects in 40% In 15% the defects disappeared *In* 15% the visual field defects increased after treatment More or less pronounced improvement of visual acuity was noted in 53% Visual acuity improved considerably in 53%, in 20% it became normal and in 13% it became worse after treatment Since about one third of the 69 patients had very large adenomas the results of transfrontal operation and postoperative radiation must be regarded as having had a satisfactory effect on the intracranial pressure and on the optic chiasma and nerves It should be stressed that also *in the group of patients treated with* radiation only, the treatment often had a good and permanent effect on the patient's vision

Observations made in the present series showed that in the calculation of visual disability expressed in percent of normal visual acuity, 20—25% should be added for coexisting visual field defects, if any Severe, disabling impairment of vision was noted after treatment in 17% of the 69 patients The corresponding figures in series on record range from 25 to 36%

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operative radiation is given, recurrences may appear several years later

After treatment with operation and radiation 58% of the patients could return to work or, if pensioners, lead a normal life for their age, while 42% were more or less severely disabled The disability was due to impairment of vision in 17% and to endocrine insufficiency in 10%

The re-examination provided an opportunity to evaluate hormonal replacement Several of the patients had been severely disabled or had died from adrenocortical insufficiency and some, even with longstanding hypopituitarism, responded favourably to replacement therapy

It is stressed that patients with chromophobe pituitary adenoma should be followed up for the rest of their lives for recurrences and target gland insufficiencies This follow-up should be done by an internist in co-operation with an neuroophthalmologist and the specialists responsible for the treatment of the tumour

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APPENDIX

Table 15 *Some data about the 131 patients with chromophobe pituitary adenoma*

Patient No Sex	Year for treatment	Anamnestic symptoms at diagnosis[1]	Duration of symptoms until diagnosis years	Age at treatment years	Age at death years	Age at the end of 1965, years	Survival years	Path histol verification	Treatment group	Year of re exam
1 F	1921	GHVS	4	25	50		25		C 1	
2 F	1922	VH	1	60	77		17		C 1	
3 F	1926	GHCV	11	49	54		5		C 1	
4 F	1927	VH	14	48	73		25		C 1	
5 M	1927	V	< 1	54	57		3		C 1	
6 M	1928	HEV	< 1	35	36		1		C 1	
7 M	1928	VH	< 1	52	53		1		C 1	
8 F	1929	VH	10	70	80		10		C 1	
9 F	1929	GVS	3	23	28		5		C 1	
10 F	1929	HVG	4	17		53	36		C 1	1960
11 M	1931	GVH	5	62	74		13	chr	A 2	
12 F	1932	VHT	4	52	75		22	"	A 2	
13 M	1932	VTH	3	63	69		6	"	C 1	
14 M	1933	V	4	47		79	32		A 2	1960
15 F	1933	VHE	3	68	80		12	mixed	C 1	
16 M	1936	HVS	8	35		65	30		B	1961
17 M	1936	GTV	4	46	68		22	chr	B	
18 F	1936	VHT	< 1	43	56		12	"	A [illegible]	
19 F	1937	GHSCT	4	23	31		8	"	C 2	
20 F	1939	GTV	14	55	69		14	"	C 1	
21 M	1939	VT	1	66	66		[illegible]	"	A 2	
22 M	1939	GTVS	7	53	54		1	"	C 1	
23 M	1940	GV	6	41		67	25		A 2	1961
24 F	1941	HV	3	54	74		20	"	A 2	1961
25 M	1944	VS	2	54		76	21	mixed	A 2	1960
26 M	1944	EHVG	5	26	39		13	chr	A 2	
27 F	1944	GHVS	4	33	40		8	[illegible]	A 2	
28 F	1944	GVH	5	43	55		12		C 2	
29 F	1945	GHVS	2	30		50	20	"	A 2	1960
30 F	1945	GV	9	46	58		12	mixed	A 2	
31 M	1945	V	2	60	74		14	chr	A 2	
32 M	1946	TGCSV	5	59	63		4		A 1	
33 M	1946	GVS	< 1	22		41	19	mixed	A 1	1960
34 F	1946	VH	1	66		85	19	chr	A 1	1960
35 M	1947	GSV	9	42		61	19		A 1	1961
36 M	1947	HVS	3	59	63		4	"	[illegible]	
37 F	1947	VHT	2	67	67		0		A 1	
38 F	1947	VH	1	62		81	18	mixed	A 2	1961
39 F	1947	VH	1	64		83	18	"	A 2	1961
40 M	1947	TGCV	6	56	56		0	chr	A 1	

[1] Initial symptom first mentioned For explanation of symbols see Chapter II

Patient No Sex	Year for treatment	Anamnestic symptoms at diagnosis[1]	Duration of symptoms until diagnosis years	Age at treatment years	Age at death years	Age at the end of 1961 years	Survival years	Path. histol. verification	Treatment group	Year of re-exam
41 M	1948	TCS	10	74	75		1		C 1	
42 M	1948	TSV	7	61		78	17	mixed	A 1	1961
43 M	1948	HV	< 1	28		45	17	chr	A 1	1960
44 M	1948	TSGV	2	52		69	17		A 1	1960
45 M	1949	VHP	1	67	72		5		A 1	
46 M	1949	VH	3	46	58		12		A 1	1960
47 F	1949	GH	10	25	31		6		B	
48 F	1949	HCV	28	58		75	16		A 1	1960
49 M	1949	GHCV	10	64	68		4		A 1	
50 M	1949	TSVH	3	65	72		7	.	A 1	
51 M	1949	GVH	12	54	58		4	mixed	A 1	
52 M	1949	VHT	< 1	51		67	16	chr	A 1	1960
53 M	1949	V	1	54		70	16		A 1	1961
54 F	1949	GV	6	32		48	16		A 1	1960
55 M	1950	TH	5	69	71		2		C 1	
56 M	1950	V	3	42		57	15	chr	A 1	1961
57 F	1950	GHVC	25	53		68	15	mixed	A 1	1960
58 M	1950	HV	< 1	29		44	15	chr	A 1	1960
59 F	1950	V	1	62	73		11		A 1	1960
60 F	1951	V	7	49		62	15		A 1	1960
61 F	1951	GV	7	41		55	14		A 1	1960
62 F	1951	V	1	53		66	14		A 3	1960
63 M	1951	V	< 1	57		71	14	mixed	A 1	1960
64 M	1952	HT	2	51		64	14	chr	A 1	1960
65 M	1952	V	< 1	47	56		9		B	
66 F	1952	VHCTS	1	57		71	14		A 1	1961
67 F	1952	STCV	10	53		67	14		A 1	1961
68 M	1952	VG	5	45	54		9		A 3	
69 F	1952	V	< 1	58		71	13	mixed	A 1	1961
70 F	1952	GTCS	10	46		59	13	chr	A 1	1960
71 M	1952	GV	5	47		60	13	mixed	A 3	1960
72 F	1952	HVST	3	66		79	13	chr	A 1	1960
73 M	1952	VHS	4	24		37	13		B	1960
74 M	1952	HV	10	46	49		3		A 1	
75 M	1952	HVC	15	30		43	13	mixed	A 1	1960
76 F	1953	GV	1	42	49		7	chr	A 1	1960
77 M	1953	GVS	1	29	37		8		A 3	1960
78 M	1953	HV	7	55	61		6		A 1	
79 M	1953	VS	14	44		56	12		A 1	1960
80 F	1954	GHV	3	20		32	12		A 1	1960
81 F	1954	GHV	5	34	38		4		A 1	
82 F	1954	GH	14	52	53		1		C 1	
83 M	1954	TCGV	5	67	71		4	mixed	A 1	
84 F	1954	VGH	1	35		47	12	chr	A 1	1960
85 M	1954	VHG	24	45	45		0	mixed	A 1	

Patient No Sex	Year for treatment	Anamnestic symptoms at diagnosis[1]	Duration of symptoms until diagnosis years	Age at treatment, years	Age at death years	Age at the end of 1965 years	Survival years	Path histol verification	Treatment group	Year of re exam
86 F	1954	V	2	58			11	chr	A 1	1960
87 M	1955	VH	3	45	45		0		A 1	
[illegible] F	1955	VH	3	65		76	11		A 1	1961
89 M	1955	TVS	1	60		71	11		A 1	1960
90 F	1955	VP	< 1	26		37	11		B	1961
91 M	1955	V	3	30		41	10		A 1	1960
92 M	1955	THSG	2	33		43	10		A 1	1960
93 M	1955	VHTGSC	1	35		45	10		A 1	1960
94 M	1955	TVC	1	64		74	10		A 1	1961
95 F	1955	HV	< 1	31		41	10	,	A 1	1961
96 F	1955	GHV	4	54		64	10		A 3	1960
97 F	1955	GVS	15	39		49	10		A 1	1961
98 M	1956	GHV	3	46		56	10	,	A 1	1960
99 M	1956	HGT	1	51		61	10		C 2	1960
100 M	1956	GV	2	52		62	10		A 1	1960
101 M	1956	GHV	9	50		60	10	,	A 1	1960
102 M	1956	GC	10	46		56	10		C 2	1960
103 M	1956	GHV	6	52		62	10		A 1	1960
104 M	1956	V	< 1	66	68		2		C 1	
105 F	1956	VS	5	48		57	9	,	A 1	1960
106 M	1956	VH	5	64		73	9		A 1	1960
107 F	1956	VH	3	53		62	9	,	A 1	1961
108 M	1957	HV	2	44		53	9		A 1	1960
109 F	1957	VT	4	66	69		3		C 1	
110 F	1957	GSHV	7	44		53	9		A 1	1961
111 M	1957	TCHVG	1	54		62	8		A 1	1960
112 M	1957	V	1	40		48	8	,	A 1	1960
113 M	1957	V	1	37		45	8		A 1	1960
114 M	1958	V	< 1	42		49	7	,	A 1	1960
115 M	1958	GTCS	13	34		41	7		C 2	1960
116 M	1958	VH	1	41		48	7		A 1	1960
117 M	1958	H	< 1	14		21	7		A 4	1960
118 M	1958	GHVC	4	37		44	7	mixed	A 1	1960
119 M	1958	GV	2	60		67	7	chr	A 4	1960
120 F	1959	GCV	6	23		30	7		A 1	1960
121 M	1959	GTVH	6	60		66	7	,	A 1	1960
122 M	1959	TGCHV	9	48		54	7		A 1	1960
123 M	1959	GSVH	2	57		63	6		A 1	1960
124 M	1959	VS	< 1	53		59	6	,	A 1	1960
125 M	1959	V	< 1	61		62	1	,	A 1	
126 F	1959	GVTSC	28	58		58	0		A 1	
127 F	1960	HV	6	60		60	0		A 1	
128 M	1960	V	1	58		58	0		A 1	
129 F	1960	VPG	5	28		33	5	,	A 1	1961
130 M	1960	V	6	68		73	5		A 1	1961
131 M	1960	V	2	56		56	0		A 1	

Table 16 — *Primary treatment and treatment for recurrence cause of death visual disturbances and radiologic changes before and after treatment of 131 patients with chromophobe pituitary adenoma*

A Combined treatment (operation and radiation)

1) *Transfrontal operation and radiation with uniform medium voltage technique*

Pat No sex	Roentgen treatment tumour dose r/days	Time until recurrence, years	Re treatment op radiation r/days	Cause of death	Visual disturbances before/after treatment: visual fields	Visual disturbances before/after treatment: visual acuity	Radiologic changes before/after treatment: sella turc. ballooned =+ tot. destr =++	typ enc height mm.
32 M	3 700/71	< 1		Chr aden +pituit insuff	5/1	III/I	+/	
33 M	2,000/20				2/1	II/O	+/+	26/
34 F	3 120/19				1/1	II/O	+/+	18/
35 M	1 500/12			Chr pituit adenoma	4/4	V/III	+/+	25/
37 F					5/	V/	++/	29/
40 M				Chr pituit. adenoma	4/	IV/	+/	33/
42 M	3 640/73				6/6	V/V	++/++	+/
43 M	3 850/75				1/1	I/O	+/+	25/
44 M	4 390/171				1/0	I/O	+/+	
45 M	4,550/66			Haemorrh. cerebri	3/4	III/II	+/	26/
46 M	3 600/68			Carcinoma ventriculi	1/4	I/II	+/+	+/
48 F	5 073/74				3/3	II/II	+/+	+/
49 M	6 170/64			Haemorrh. cerebri	1/1	II/II	+/	
50 M	3 870/69			Pituitary insuff	4/4	IV/V	++/	28/
51 M	3 600/61			Infarctus myocardii	1/1	II/II	+/	
52 M	4 200/61				2/5	IV/II	++/++	24/0
53 M	3 500/120				5/1	O/O	+/+	25/
54 F	5 040/78				2/1	II/O	+/+	26/
56 M	1 600/15	11	+ 3 700/26		5/3	III/II	+/+	22/23
57 F	3 720/60				2/1	I/O	+/+	18/
58 M	3 600/55				1/0	I/O	+/+	18/
59 F	4 500/60			Bronchopn.+Embol pulm	5/1	I/I	++/++	25/
60 F	4 200/62				6/6	V/V	+/+	
61 F	4 020/60				2/1	II/O	+/+	24/0
63 M	4 080/67				2/5	II/IV	+/+	+/0
64 M	4 860/77				1/0	O/O	+/+	
66 F	5 000/175				3/1	III/II	++/++	31/
67 F	4 320/28				3/5	II/IV	+/+	28/
69 F	3 900/27				2/4	II/IV	+/+	18/
70 F	5 460/84				1/0	O/O	++/++	
72 F	3 250/22				1/1	II/II	++/++	23/
74 M	4,410/35	< 1		Chr aden.+Pituit insuff	6/6	V/V	++/	55/
75 M	5 170/36				1/0	O/O	+/+	30/0
76 F	3 550/25			Infarctus myocardii	2/2	IV/V	+/+	24/
78 M	4,350/68			Carcinoma epipharyng	5/1	II/I	+/+	23/0

For explanation of symbols see Chapter IV

Pat No sex	Roentgen treatment, tumour dose r/days	Time until recurrence years	Re op	treatment radiation r/days	Cause of death	Visual disturbances before/after treatment: visual fields[1]	visual acuity[1]	Radiologic changes before/after treatment: sella turc ballooned =+, tot destr =++	typ enc. height mm
79 M	3 430/21					2/1	III/II	+/+	28/
80 F	4,380/72					1/1	I/I	+/+	21/
81 F	4 280/74				Adrenocort insuff ?	4/6	V/V	+/	28/
83 M	4,380/33				Haemorrh cerebri	2/2	IV/II	+/+	+/
84 F	3,720/28					4/2	II/II	o/	28/
85 M					Chr pituit adenoma	5/	IV/	+/	60/
86 F	4,220/30					1/1	II/II	+/+	23/
87 M					Chr pituit adenoma	4/	IV/	+/	32/
88 F	3,900/32					1/1	II/II	+/+	27/
89 F	3,540/70					1/5	II/V	+/+	17/
91 M	4 080/64					1/1	II/O	+/+	+/
92 M	2 900/26	6	+	1,950/18		1/1	O/O	+/+	+/
93 M	4 080/69					4/1	II/II	+/+	31/
94 M	4,140/77					1/1	II/II	+/+	
95 F	4 220/69					5/1	IV/IV	+/+	12/
97 F	4 380/65					1/0	IV/O	+/+	
98 M	3,800/36					1/1	II/I	+/+	+/
100 M	3 640/35					4/6	IV/V	+/+	+/
101 M	3 640/33					2/2	II/II	+/+	21/
103 M	4 540/83					1/0	II/O	+/+	21/
105 F	4 420/38					4/4	II/II	+/+	+/
106 M	4 140/36					5/5	III/II	+/+	24/
107 F	3 970/40					1/1	II/O	+/+	+/
108 M	4 100/37					4/1	I/O	+/+	20/
110 F	3,810/29					1/1	II/O	+/+	22/
111 M	3,500/32					1/0	I/O	+/+	20/
112 M	3,460/27					1/1	O/O	+/+	16/0
113 M	2,720/27					2/5	II/II	+/+	19/0
114 M	4,080/76					2/1	II/II	++/++	21/0
116 M	3 780/78					1/0	II/O	+/+	15/
118 M	4 220/73					3/0	II/O	+/+	18/
120 F	4 220/61					4/4	II/II	+/+	+/
121 M	3,550/27					1/1	II/O	+/+	+/
122 M	3,170/26					1/1	I/O	+/+	27/
123 M	3 170/27					5/4	III/II	+/+	19/
124 M	3 170/27					1/1	II/I	+/+	24/
125 M					Chr pituit adenoma	4/	II/	+/	25/
126 F					Chr pituit adenoma	5/	II/	++/	26/
127 F					Chr pituit adenoma	1/	III/	++/	23/
128 M					Chr pituit adenoma	1/	II/	+/	+/
129 F	3 000/22					0/0	O/	+/+	17/
130 M	4 320/76					4/4	II/II	+/+	20/
131 M					Chr pituit adenoma	1/	II/	++/	19/

Pat No, sex	Roentgen treatment, tumour dose r/days	Time until recurrence years	Re treatment op	Re treatment radiation r/days	Cause of death	Visual disturbances before/after treatment: visual fields	visual acuity[1]	Radiologic changes before/after treatment: sella turc ballooned =+ tot destr =++	typ enc height mm.
2) *Transfrontal operation and radiation with old technique*									
11 M	tum dose?				Haemorrh cerebri	4/4	V/V	+/	
12 F					Cardiac decompens	4/6	V/V	+/	
14 M		25+5	+	+		2/2	II/III	+/+	+/32
18 F		7	+	tum dose?	Chr pituit. adenoma	2/4	IV/V	+/	+/
21 M					Chr pituit adenoma	2/	V/	+/	
23 M						2/1	II/II	+/+	
24 F					Haemorrh cerebri	1/1	II/II	+/+	
25 M						4/1	IV/II	+/+	+/
26 M		11			Chr pituit adenoma	4/5	II/II	+/+	+/40
27 F		8			Chr pituit. adenoma	4/6	V/V	+/	+/
29 F		4	+	3 700/60		1/0	I/O	+/+	13/13
30 F		11		5 040/70	Chr pituit adenoma	2/2	II/II	+/+	+/22
31 M		13		4 550/72	Chr pituit. adenoma	1/6	I/V	+/	
38 F						1/1	II/II	+/	+/
39 F						1/1	III/III	+/+	
3) *Transfrontal operation (biopsy only) and radiation*									
62 F	3 600/15	1	+			2/2	II/II	+/+	+/
68 M	6 010/74				Pituit insuff	1/1	II/O	++/++	26/
71 M	4 610/40					4/4	II/II	++/++	25/13
77 M	4 290/34	8			Chr pituit adenoma	1/0	II/O	+/+	20/12
96 F	5 350/14					5/5	II/II	++/++	27/20
4) *Transspenoidal operation and radiation*									
117 M	2 800/21	< 1	+	1 580/16		1/0	II/O	+/+	29/29
119 M	4 320/72					1/1	II/I	++/++	23/
■ *Surgical treatment only*									
16 M						5/3	II/II	+/+	
17 M		> 1	+	tum dose?	Haemorrh cerebri	4/6	V/V	+/	
36 M		4	+		Chr pituit adenoma	5/5	II/II	++/++	26/26
47 F		2			Chr pituit. adenoma	5/5	I/II	++/++	35/45
65 M		3	+	4 000/35	Pituit insuff	3/6	II/V	+/	+/
73 M		13	+	3 130/31		4/3	II/II	+/+	35/0
90 F						2/1	IV/O	0/+	22/

Pat No sex	Roentgen treatment tumour dose r/days	Time until recurrence years	Re op	Re treatment radiation r/days	Cause of death	Visual disturbances before/after treatment: visual fields[1]	visual acuity[1]	Radiologic changes before/after treatment: sella turc ballooned =+ tot destr =++	typ enc height mm
					C *Roentgen treatment only*				
					1) *Patients with compression of the optic chiasma*				
1 F	tum dose?	12		tum dose?	Mors subita—causa?	4/4	IV/III	+/	
2 F	,,	4		,	Haemorrh cerebri	4/1	II/III	+/	
3 F	,				Chr pituit adenoma	4/4	V/V	+/	
4 F	,				Pituit insuff	2/2	II/II	+/	
5 M	,,				Chr pituit adenoma	2/4	II/II	+/	
6 M	,,				Chr pituit adenoma	5/5	V/V	+/	
7 M	,,				Chr pituit adenoma	4/6	V/V	+/	
8 F					Haemorrh cerebri	4/4	V/IV	+/	
9 F	,				Chr pituit adenoma	6/4	V/II	+/	
10 F	,,					3/3	IV/II	+/+	
13 M					Metast carcinoma	4/4	V/V	+/	
15 F	,				Haemorrh cerebri	1/5	II/I	+/	
20 F		9	+	tum dose?	Carcinoma coli	1/4	II/II	+/+	
22 M	,				Chr pituit adenoma	5/5	V/V	+/	
41 M	4 800/78				Chr aden +pituit insuff	1/1	II/II	+/	25/
55 M	7,000/85				Chr pituit adenoma	5/0	O/O	+/	24/
88 F	4,600/31				M sub (thrombocytopenia)	1/1	II/O	+/	18/
104 M	4 200/36				Chr pituit adenoma	4/2	IV/V	+/	+/
109 F	3 500/32				Chr pituit adenoma	1/1	IV/II	++/	19/
					2) *Patients without compression of the optic chiasma*				
19 F	tum dose?		+		Pituit insuff	0/5	O/III	+/	
28 F		6	+	5,600/75	Chr aden +pituit insuff	1/4	V/V	+/+	+/27
99 M	4 320/66					0/0	O/O	+/+	14/7
102 M	4 080/38					0/0	O/O	++/++	0/
115 M	3 500/63					0/0	O/O	+/+	0/0

Table 17 *Data about target gland status in 131 patients with chromophobe pituitary adenoma before/after treatment*

o = normal, no insufficiency, (+) = probably pathologic or insufficient + = pathologic or insufficient, ? = interpretation impossible

Pat No Sex	Loss of potency Amenorrhoea age at years	Sex hair reduced	Testicular atrophy sexual undeveloped	FSH[1]	Cold intolerance	BMR, per cent	Cholesterol mg %	Thyroidal uptake—urinary excretion of I^{131} per cent	PBI μg %
A *Combined treatment (operation and roentgen treatment)*									
1) *Transfrontal approach and uniform medium voltage roentgen technique*									
32 M	+/	+/+			+/+	−25/			
33 M	+/+	(+/+)	o/o	/1	o/o	−27/−39	/379		/ 3 8
34 F		/+		/2	/o	/− 4	/308		/ 3 7
35 M	+/+	(+/+)	o/o	/4	o/o	−14/−23	/297		/8 o
37 F	48/								
40 M	+/	+/	+/		+/	−20/			
42 M	/+	+/+	/+	/4	/o	/− 3	/192		/5,2
43 M	o/o	o/o	o/o		o/o	−12/−10	/232	/37−54	/8,1
44 M	o/+	+/+	/+	/4	o/+	/−32	/434		/3 o
45 M		o/		/2	/o	/−20	/244	/56−49	
46 M	o/+)	(+ /+	o/+		/+	/−35	/342		
48 F	50/+	o/+		/2	/+		/310	/32−32	/3 4
49 M		o/	o/		+/	/− 9			
50 M		+/+			/+	− 3/ 35	/17-		
51 M	+/	(+ /+	+/+			− 4/	203/		
52 M	o/o	o/o	o/o	/2	/o	/−30	/45-		
53 M	o/ +)	o/o	o/o	/4	/o	/+ 4	/230		
54 F	26/+	o/o		/4	/+	/−18	/280		
56 M	/o	o/o	o/o	/2	o/o	−13/−15	/308	/-1 58	/7,5
57 F	28/+	+/+		/4	+/+	−10/−25	/276	/20−54	
58 M	o/+	o/+	o/+	/3	o/o	− 4/+ 4	/325	/42−46	/6 o
59 F	49/+	o/o				/−18	/298		/4 8
60 F	42/+	+/+		/4	o/+	− 6/−26	/354		/3 5
61 F	34/+	o/o		2/2	/+	/−11	/304	/44−36	
63 M	o/ +)	o/o	o/o	/-	o/o	6/−13	/322		/4·3
64 M	/+	+/+	/+		/+	−-3/−27	/211		
66 F	50/+	+/+		2/2	+/o	−27/−11	/304		/4 7
67 F	48/+	+/+	/+	/4	+/+	−19/ 16	240/295	/49−27	/5 o
69 F	(40)/ [2]	o/+			/+	22/−40	270/405		
70 F	54/+	(+/+)	+/+	/4	+/o	−16//19	245/376		/5 2
72 F	45/+	+/+		/4		−16/−-0	/370		/4 1
74 M		+/+		4/4	/+	−11/−44	180/-55		/2 4
75 M	o/+	o/+	o/+	/4	+/+	6/−27	157/182		/2 5
76 F	(38) [2]	o/+)		1/1	/+	−-2/−25	225/425	/22−46	
78 M	/+	o/+	/+		/+)	−14/−30	/160		

[1] 1 = FSH >40 2 = $>10<40$ 3 = ~ 10 4 = <10 MUU [2] Hysterectomized

[illegible]	Blood pressure mm Hg	4 hour water load test	Thorn eosinophil test	Insulin tolerance test	17 KS mg/24 h	17 KGS mg/24 h	Plasma corticosteroid level	Hypopituitary picture	Interpretation of target gland status GTA/GTA
+/+	140— 70/							+/+	+ + + / + + +
o/o	140— 90/120— 80	/o			/111	/130		o/o	o + / o + ■
o/o	150— 90/170— 80	/+			/ 50	/ 99		o/o	/ + o o
o/o	130— 70/140— [illegible]	/+			/174	/152	/o	o/o	+ o / + o o
+/	120— 70/							+/	/
+/	170—130/							+/	+ + /
+/+	120— 80/150— 80	/+			/ 04	/ 35	/+	+/+	(+) / + ■ +
+/o	130— 80/120— 80	/o		/o	/184	/ 42		o/o	o o / o o o
+/+	140— 90/150—100	/+			/ 24	/ 74		+/+	(+) / + + +
o/o	160— 90/140— 80		/o	/o	/ 54				o / o o o
/+	110— 90/110— 50	/+	?/		/ 25			o/+	■ / + + +
o/+	150— 90/160— 90	/+	/o		/ 28	/ 68		/+)	/ + (+)(+)
/+	180—100/		/+	/o	/ 40			/+)	/ o +
/+	110— 70/110— 80		/+	/+	/ 17			+/+	(+) o / + + +
	170—110/							+/+	+ ■ / +
+/+	140— 90/190—110	/+	/o	/o	/ 63	/ 92		o/o	o / o + +
o/o	160— 90/180— 90	/o		/o	/127	/159	/o	o/o	■ / o o o
o/o	120— 80/130— 70	/o	P	/o	/ 44	/ 88		o/+)	+ / + + o
o/o	140— 90/160—100	/o			/104	/155	/o	o/o	■ o / o o o
o/o	160—100/190—100	/+	/o		/ 29	/ 64		o/o	+ o / + + o
o/o	130— 80/120— 80	/o	P	/o	/137	/150		o/+	■ o / + ■ o
	200—110/180— 90	/o	/o		/145			o/o	o o / o o
	130— 90/130— 80				/ 18	/ 40		/+)	+ o / + +
o/o	120— 90/140—100	/+	P	/o	/ 59	/103		o/o	+ / + + o
o o	/210—100	/+			/ 73	/113		o/o	o o / o o o
+/+	140— 90/110— 70				/ 75			/+)	(+) / + + +
(+/o	160—110/.00—110	/o	+/+		54/ 11	/ 70	/o	o/o	+ + o / + o o
+/+	170—100 180—100	/+	?/?		29/ 05	/ 20	/+	/+	o / + o +
+/+	130— 80/130— 80		+/+		77/ 34	/ 39		/+	(+)(+)/(+) + +
+/o	/130— 70	/o	o o	/o	31/ 14	/ 32		o/o	+ o o / + o o
	110— 80/130— 70	/+	? o		40/ 26	/ 69		+/+	(+) o / + (+)(+)
/+	150—100/130—100		?/o		67/ 17				(+) o o / + + +
o/+	110— 70/110 80	/+	/o		89/ 27	/ 56		o/+	o o o / + + +
o o	150—120/140— 80	/o	o/o	o	32 54	/ 72		o/o	o (+) o / o + o
o/+	160—100/130— 70	o/+	/o	/o	77/ 54			o/+	o o o / + (+)(+)

Pat No Sex	Loss of potency Amenorrhoea age at years	Sex hair reduced	Testicular atrophy sexual undeveloped	FSH[1]	Cold intolerance	BMR, per cent	Cholesterol mg %	Thyroidal uptake—urinary excretion of I^{131} per cent	PBI μg %
79 M	o/o	(+4/4+)	o/o	/3	o/o	— 9/—18	/253	/29—47	/5 6
80 F	17/+	o/o	/+	/4	o/o	—15/—11	204/236	40—42/49—44	/4 3
81 F	29/+	(+4/4+			o/o	—12/—26	241/282	/51—36	
83 M	+/+	(+/+	+/+		+/+	—30/—27	265/272	/42—34	
84 F	34/o	o/o	o/o		o/o	— 7/	216/		
85 M	+/	+/	+/		+/	—23/	232/		
86 F	46/+	(+/+	/	/2	o/o	—12/—16	246/246	33—40/	/4 1
87 M	o/	o/	o/			—24/	255/	33—18/	
88 F		(+/+	/+	/4	o/o	—16/— 8	/280	/53—54	/5 8
89 M	/+	(+/+	o/o	/2	o/o	—16/+ 5	270/286	/20—50	
91 M	o/o	o/o	o/o	/2	o/o	—12/— 9	/282	/40—55	/5 6
92 M	(+/+	+/o	o/o	4/4	o/o	— 6/—16	292/252	/36—43	6 5/6 3
93 M	o/+)	(+/+)	o/o	/2	(+/+)	— 4/—18	223/300	/34—41	
94 M	o/o	o/+	o/+)		+/+	—28/—32	323/320	/11—56	
95 F	o/o	o/+)		/2	o/o	—10/—13	222/277	/28—57	/6 4
97 F	28/+	(+/+)			o/+	—12/—32	245/274		5 2/3 0
98 M	+/+	o/o	/+	/4	o/o	—22/+ 3	338/280	/22—60	/6 5
100 M	o/+	o/+	o/+	/4	o/+	—10/—17	256/257		/5 2
101 M	+/+	o/+	o/+	2/4	o/+	—26/—20	235/114	/26—45	
103 M	+/+	o/+	o/+	4/4	o/+	— 7/—23	280/279	/55—35	6 0/3 5
105 F	prim	(+/+)	+/+	/2	o/o	— 3/—20	/315		/4 7
106 M	/+)	o/o	o/o	/1	o/o	—14/—13	225/220	/45—43	/8 1
107 F	46/+	o/o	o/o	/2	o/o	— 7/+ 2	/343	/46—32	/7 8
108 M	/+	o/o	o/o	/1	o/o	/— 3	/-57	/35—41	/4 7
110 F	37/+	(+/+)		/2	o/o	—15/+ 7	403/230	/42—41	
111 M	(+/+	/+	/+	/1	+/o	+ 1/+ 4	149/261	36—42/	/6 3
112 M	o/o	o/o	o/o	/2	o/o	—11/ o	369/393	52—37/	/5 6
113 M	o/o	o/o	o/o	1/2	o/o	—17/—15	239/338	47—31/50—32	6 4/5 6
114 M	o/o	o/o	o/o	/2	o/o	—10/— 2	272/307	/40—39	/4 3
116 M	o/o	o/o	o/o		o/o	/—15	243/296	/31—44	/4 3
118 M	+/+	o/o	o/o	4/	+/+	—20/— 4	366/364	35—46/	5 5/8 4
120 F	17/+	(+/+)	o/o	3/	+/o	—15/—11	392/		
121 M	+/+	(+/+)	o/o	/4	o/o	+ 1/— 5	279/294	/42—36	4 4/5 0
122 M	+/+	+/+	+/+	4/4	+/+	—18/	299/	34—45/	6 4/
123 M	+/+	(+/+	+/+		o/+	—22/— 5	225/276	27—40/26—46	/5 0

[1] 1=FSH >40 2=$>10<40$ 3=~10 4=<10 MUU   [2] Hysterectomized

T redae we kne e	Blood pressure mm Hg	4 hour water load test	Thorn's eosinophil test	Insulin tolerance test	17 KS mg/24 h	17 KGS mg/24 h	Plasma corticosteroid level	Hypopituitary picture	Interpretation of target gland status GTA/GTA
o/+	160—100/140— 90	o/o			7 8/ 7 7	/ 9 3		o/o	o o o / o o o
o/o	130— 70/110— 70	o/o	o/o		12 7/ 7 6	18 6/ 7 6		o/o	+ o o / + o o
o/o	180—120/140—100	o/o	?/	/o	6 0/ 4 9				+ o o / + o o
+/+	130— 90/180—100	/+	?/		2 7/ 2 3	/ 4 2		+/+	+ + (+)/ + + +
o/o	120— 80/	o/	?/		16 2/			o/o	+ o o / o o o
+/	130—100/	+/	+/	o/	1 3/			+/	+ + + /
o/o	140— 90/140— 80	o/o	?/	o/o	9 2/ 4 1	/ 7 9		o/o	o o / + o o
o/	150—120/	+/o	?/	o/	11 3/			o/	o (+)(+)/
o/o	240—130/160—100	o/+	?/	o/	1 3/ 3 8	/ 8 2		/+)	o o / + o o
+/o	110— 60/180— 90	+/o	?/	o/	/ 6 3	/ 8 6		(+/+)	o o (+)/ o o o
o/o	120— 80/120— 80	/o	o/	/o	/20 6	/13 3		o/o	o o o / o o o
+/o	120— 80/	+/+	+/		3 8/ 2 0	3 6/ 3 8		(+/+	+ o + / + o +
+/o	120— 80/120— 80	o/o	?/	o/o	10 2/12 3	/13 6		o/o	o o o / o (+) o
+/+	150— 90/160— 80	+/+	/+	o/	3 7/ 2 3			o/+)	o + + / + + +
o/o	110— 70/130— 80	o/o	?/	o/o	7 3/ 5 6	/ 6 1		o/o	
+/o	120— 80/120— 80	+/+	o/	o/	6 8/ 1 3	10 1/ 3 1		o/o	+ o + / + + +
o/o	170—110/150— 70	o/o	?/	o/o	12 7/ 7 8	/11 7		/+)	+ o o / + o o
o/+	140— 90/130—110	+/+	?/o	+/	8 0/ 1 7	/ 5 6		o/+)	o o + / + + +
o/+	160—100/190—100	+/+	?/	o/	8 7/ 1 9	/ 3 6		o/+)	+ + + / + + +
o/+	/120— 80	+/+	o/o	/o	6 4/ 4 0	3 3/ 6 7		o/+	+ o + / + + +
o/o	110— 70/130 70	o/o	?/	o/o	6 6/ 5 3	/11 6		(+/+	o o / + o o
o/o	140— 80/170 80	o/o	?/	/o	13 9/ 8 3	/10 2	/o	o/o	o o o / o o o
o/o	140— 80/130— [illegible]	+/o	?/	o/o	9 7/ 3 3	/16 0	/o	o/o	o o / + o o
o/o	130— 90/120— 80	/o			/13 7	/14 1		o/o	o o / o o o
+/o	160—100/160—110	o/o	/o		4 1/ 4 2	6 8/ 7 8	/o	o/o	+ o o / + o o
+/+	130— 70/140— 90	+/+		/o	/ 3 6	/ 4 8		/+	+ o + / + o +
o/o	110 70/120— 70	o/o	?/		11 6/11 1	/18 1		o/o	o o o / o o o
o/o	120 80/150— 90	o/o		o/	13 8/13 4	16 8/17 1		o/o	o o o / o o o
o/o	140 90/110— 70	+/o		/o	25 3/19 3	/16 6		o/o	o o o / o o o
o/o	140—100/	/o			/15 4	/18 6		o/o	o o o / o o o
o/o	120— 80/100 80	o/+	+/o	/o	16 8/ 5 8	9 2/ 8 9		o/o	+ o o / + o (+)
o/o	140— 90/120— 80	+/+	?/	+/	12 6/ 2 2	4 6/ 3 3		o/o	+ + + / + + +
+/+	120— 80/150— 80	+/+	?/	o/o	4 4/ 2 7	2 9/ 8 0	/+	o/o	+ o + / + o +
+/o	90— 60/110— 80	+/+		+/	1 3/	3 5/		+/+	+ + + / + + +
o/o	150—100/150— 90	+/+			5 6/ 2 3	4 3/ 2 3		+/+	+ o o / + o +

Pat No Sex	Loss of potency Amenorrhoea age at years	Sex hair reduced	Testicular atrophy sexual undeveloped	FSH¹	Cold intolerance	BMR, per cent	Cholesterol mg %	Thyroidal uptake—urinary excretion of I^{131} per cent	PBI μg %
124 M	o/o	(+/+)	o/+)	/4	o/+	−23/+11	239/311		/6 3
125 M		o/	o/	4/	o/	−11/	195/		
126 F	30/	(+/		4/	+/	−18/	290/		6 3/
127 F	(43)/*	+/			o/	−12/	272/	54−42/	
128 M	o/	o/	o/		o/	−11/	150/		
129 F	o/27	o/o		3/2	o/o	−16/−15	193/248	29−54/	4 5/4 3
130 M		o/+)			o/+	−18/−14	257/185	/27−35	3 8/5 7
131 M		o/	o/			−18/	325/		6 6/
2) Transfrontal approach and radiation with the old technique									
11 M	+/	(+/+			o/	−13/			
12 F	52/+					+14/			
14 M	o/+)	o/o	o/o	/4	o/o	− 2/−24	/286		/3 3
18 F	o/47					−10/−15			
21 M			+/		(+/	−20/			
23 M	+/+	o/+	o/+		o/+	+ 2/−18	/345		
24 F	49/+	+/+	+/+		o/+	−35/−13	/375		/2 9
25 M	/+)	(+/+	o/o	/4	o/o	− 5/−16	/322		/3 7
26 M	(+/+	+/+	+/+	/4	o/+	− 3/− 25	/350		
27 F	29/+		(+/		o/	− 6/			
29 F	28/o	(+/+)	o/o	/2	o/+)	− 3/−22	/242	/40−45	
30 F	27/+	o/				−13/−21	/225		
31 M	o/o	o/+	o/+			− 7/−35	/385		/4 4
38 F	52/+	(+/+			o/o	+10/			
39 F	53/+	o/o	/+	/1	o/o	−20/+10	/250		/5 6
3) Transfrontal approach (biopsy only) and radiation									
62 F	52/+	o/(+)		/4	o/o	/+ 2	/218		/4 7
68 M	+/+	o/+	(+/+		o/+	−20/−20	187/.80	30−55/41−23	
71 M	+/+	(+/+)	/+	/4	o/+	−10/−38	179/218	/44−46	/4 1
77 M	o/+)	(+/+)	(+/+)		o/o	−16/−16	188/	/49−24	/4 5
96 F	43/+	o/o		/2	o/+	−10/−26	365/477	30−39/24−50	/3 4
4) Transsphenoidal approach and radiation									
117 M	/+	(+/+	(+/+	1/4	o/+	−2./−27	20./186	.9−58/20−79	/2 7
119 M	(+/+	o/o	o/o	/4	/o	− 9/− 4	293/298		/4 6

¹ 1=FSH >40 2=>10<40 3=~10 4=<10 MUU   * Hysterectomized

[illegible]	Blood pressure mm Hg	4 hour water load test	Thorn eosinophil test	Insulin tolerance test	17 KS mg/24 h	17 KGS mg/24 h	Plasma corticosteroid level	Hypopituitary picture	Interpretation of target gland status GTA/GTA
(+/+)	130— 70/140— 90	+/+	?/		3 3/ 2 3	4 9/ 8 4		o/+)	o o (+)/ o o (+
o/	160—100/	+/			7 8/	5 5/		o/	o o o/
+/	130—120/	+/		o/	9 3/	8 8/		o/	+ o (+)/
o/	180—100/	+/			2 9/	6 1/		(+/	o + /
o/	140— 90/	+/		o/	6 6/	3 o/		o/	o o + /
o/o	120— 80/130— 80	o/o		o/	5.4/ 4 2	12 6/15 5	/o	o/o	+ o o / + o (
+/+	120— 70/110— 60	+/		o/	15 2/ 5 7	6 4/ 3 5	/+	o/+	■ + (+)/(+) + +
o/	130—100/	+/			4 9/	11 o/		o/	o o o/
	110— 80/							+/+	+ o /
+/	180—100/								■ /
/o	120 70/	/+			/ 3.4	/ 7 2		o/o	o o / ■ (+)
	110— 70/120 80								o / o
+	120 70/							+/	+ (+) /
/+	100 70/160 90	/+	/+		/ 1 7			(+/+	+ o / + +
/+	160—110/200 110					/ 4 9	/+	/+	/(+) +
/o	120 80/130— 90	/+				/ 4 0		o/(+)	■ ■ /(+)(+)(
/+	90 60/		/+			/ 4 2		+/+	+ o / + +
	140 80/150 90								+ o / +
o/o	150—100/150 90	/o	/o	/o	/ 9 1	/17 o		o/o	+ o / o (+)
	120 90/110— [illegible]	/+	/+		/ 8 8				+ / + (+)
	110 70/240—120		/o		/ 3 6	/ 3 6			o o / + (+)
o/o	130 90/							o/o	o / ■
o/o	160 90/210 110	/o			/ 3 6	/10 8	/o	o/o	o / o o
o/o	170 100/140 90	/+			/ 4 3	/ 8 4		/+	o / + o(
o/+	130 80/ 90 50	/+	o/		5 1/ 1 8	/ 1 9		/+	+ o (+ / + +
o/+	130 80/140 80	/+	?/?	/o	10 1/ 5 6	/ 6 6		/+	+ o o / + +
o/+	140— 90/100 60	/+	/+		5 4/ 4 2	/ 7 4		(+/+)	+ o / + +
o/o	180— 90/180— 90	o/o	?/		15 2/ 5 7	/10 0		o/o	o o / + +
o/o	100 60/110— 80			/+	2 2/ 6 7	/14 9		o/+)	(+) o o / + +
o/o	130 80/180— 90			+/o	7 6/ 6 7	/10 2		o o	o o + / + o

Pat No Sex	Loss of potency Amenorrhoea age at years	Sex hair reduced	Testicular atrophy sexual undeveloped	FSH[1]	Cold intolerance	BMR per cent	Cholesterol mg %	Thyroidal uptake—urinary excretion of I^{131} per cent	PBI µg %
B *Surgical treatment only*									
16 M	o/+	(+/+	o/+	/4	o/o	−17/− 1	/340		/6 6
17 M	+/+	(+/+)	/+	/4		/−18	/260	/40−44	
36 M	o/o	(+/+	o/o		o/o	+ 8/− 7			
47 F	prim		+/+	2/	o/	− 8/			
65 M	o/+	o/+	o/+	2/	o/+	/−28	/250	/27−56	
73 M	o/o	(+/+)	o/o	/1	o/o	−13/− 1	224/372		/5 2
90 F	o/o	o/o	o/o		o/o	/+ 9	265/265	/27−42	/6 5
C *Roentgen treatment only*									
1) *Patients with compression of the optic chiasma*									
1 F	21/+	+/+	+/+			/− 6			
2 F						/−25			
3 F	38/+				+/				
4 F	48/+	/+							
5 M									
6 M									
7 M									
8 F						/−13			
9 F	20/+	(+/+	+/+						
10 F	16/+	+/+	+/+	/3	/o	/− 2	/254		/4 0
13 M						/− 2			
15 F									
20 F	41/+	o/				+ 8/			
22 M	+/	+/+	+/+						
41 M		+/+	+/+			−10/−16	/400		
55 M									
82 F	38/+	o/				−14/−16	/280		
104 M	o/					− 9/− 2	302/		
109 F	50/+					−27/	218/		
2) *Patients without compression of the optic chiasma*									
19 F	19/+	o/+	o/+			−24/− 21			
28 F	(40)/[2]					/− 8	/244		
99 M	(+/+	(+/+	(+/+	/3		−11/−30	220/	/68 − 27	
102 M	+/+	o/o	o/o	4/		−38/−21	275/134	7−41/	
115 M	(+/+	(+/+)	+/+	4/		−23/−18	354/	24−53/	4 1/

[1] 1=FSH >40 2=>10<40 3=~10 4=<10 MUU

[2] Hysterectomized

Tired weakness	Blood pressure mm Hg	4 hour water load test	Thorn eosinophil test	Insulin tolerance test	17 KS mg/24 h	17 KGS mg/24 h	Plasma corticosteroid level	Hypopituitary picture	Interpretation of target gland status GTA/GTA
0/0	140–80/180 120	/0		/0	/29	/135	/0	(+/+	■ ■ /+ o o
+/+	120–70/170–90	/+			/27	/19		+/+	+ /+ + +
+/	190–110/							0/0	o ■ /+ o
0/	140–90/				139/			+/+	+ o o/+
/+	130–80/130–90	/+	/0	/0	/62	/98			■ ■ /+ + +
0/0	130–90/120–80	/0	?/?	/0	93/163	/185		0/0	o o o/o o o
0/0	120–90/130–90	0/0	/?		/152	/226	/0	0/0	o ■ o/o o o
+/		/0						+/+	+ /+
+/									+ /+
/+								/+	o / + +
								/+	/
									/
+/								+/+	/
/0	100– /	/+		/0	/22	/59		+/+	+ /+
									+ /+ o(+)
								/+	/
+/	/190–100	0/							+ o/
/+								+/+	+ /+ + +
+/+	170–80/							+/+	+ + +/+ + +
	120 80/								/
0 0	150 90/180 100	/0	?/		16/				+ o /+ o o
0/	140 90/	+/		0/	/17				o o(+)/
0/	140–80/	0/			71	/37			(+) o/
/+	100– /							/+	+ /+ + +
	230 140/								/
+/+	150–80/120–80	+/+	?/	0/	57/92	/84		(+/+	+ o +/+ + +
0/+	120 80/120–80	0/+		0/	40/76	/98		+/+	+ + o/+ + +
+/+	120–70/120–80	/+			61/80	78/107	/+	+/+	+ + o/+ + +

ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 453

INTRAVENOUS GLUCOSE TOLERANCE IN MYOCARDIAL INFARCTION, ANGINA PECTORIS AND INTERMITTENT CLAUDICATION

by

FREDRIK WAHLBERG

Accompanies Vol. 180

STOCKHOLM 1966

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From the Department of Medicine Karolinska Institutet
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INTRAVENOUS GLUCOSE TOLERANCE
IN
MYOCARDIAL INFARCTION ANGINA PECTORIS AND INTERMITTENT CLAUDICATION

by

FREDRIK WAHLBERG

In collaboration with Lars A Carlson
(Chapter VII)

STOCKHOLM 1966

Tryckeri Balder AB Stockholm 1966

To Helen Wahlberg

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I

INTRODUCTION

Clinical manifestations of ischaemic vascular disease may develop throughout the body the main target organs being the heart legs brain and the kidneys Unfortunately the symptomatology is often nonspecific and diffuse and objective diagnostic procedures of limited value or lacking which complicates the study of some occurring manifestations Therefore the present study on intravenous glucose tolerance in ischaemic cardiovascular disease (ID) has been restricted to myocardial infarction angina pectoris and intermittent claudication because these conditions are relatively well and uniformly defined and diagnosed the world over Although they are generally referred to as ischaemic or synonymously atherosclerotic vascular diseases their relation to either ischaemia or atherosclerosis per se is not clear

Most research work regarding the metabolic events possibly responsible for the development of ID has been concerned with lipid metabolism It has been shown that its manifestations are statistically correlated to elevated serum levels of cholesterol and triglycerides (Biorck et al 1956 Albrink & Man 1959 Carlson 1960 Kannel et al 1961 Keys et al 1963 Epstein et al 1965) On the other hand it has also been found that there is an overrepresentation of diabetics in myocardial infarction (Levine & Brown 1929 Clawson & Bell 1949 Wright et al 1954 Eckerstrom 1951 Linden 1952 Ekvall 1955 Sievers et al 1961 Wahlberg 1963 reviews by Plotz 1957 Schettler 1961 Hudson 1965) and intermittent claudication (Dry & Hines 1941 Lisa et al 1942 Bell 1950) In spite of this relatively small attention has been paid to carbohydrate metabolism in patients with ID in the absence of overt diabetes Diabetes is a complex metabolic disease involving not only carbohydrate metabolism but also lipid and protein metabolism. However the causal roles have as yet not been established as regards either lipid or carbohydrate metabolism in ID neither in diabetics nor in non diabetics Furthermore it is not known whether essentially differing metabolic pathways lead to ID in either condition

Ischaemic disease of the heart and the legs presents essentially the same clinical picture in diabetics and non diabetics Their arterial vascular changes appear morphologically to be of the same type as regards atherosclerosis but in the small arteries and arterioles the diabetics more often than the non diabetics may have an additional angiopathy consisting of endothelial proliferations and depositions of PAS positive material according to Goldenberg et al (1959) Blumenthal et al (1960) and Pedersen & Olsen (1962) The latter findings have been questioned by Strandness et al (1964)

Cardiovascular disease in diabetes mellitus varies considerably as regards the time of its appearance and progress in relation to the chemical severity of the disease e g measured as hyperglycemia need of insulin or tendency to keto-acidosis On account of this it was thought possible that also abnormal carbohydrate metabolism manifested

II

MATERIAL

The following groups of subjects were studied

A *Subjects with ischaemic disease* of the heart and legs manifested by *myocardial infarction angina pectoris* or *intermittent claudication*

B *Subjects without clinical signs of cardiovascular disease* who will be referred to as *controls*

C *Subjects with clinical or* synonymously *overt diabetes mellitus*

Available hospital records and all patients have been examined by myself

A *Subjects with ischaemic disease (ID)*

1 190 patients who were admitted acutely for their *first myocardial infarction* in the Medical Department of the Seraphimer Hospital They were discharged alive and subsequently followed since the start of the present study in November 1960 They represent the total number of such patients from the hospital from this time on until the end of November 1965 10 were left out for the following reasons 5 male patients not living permanently in Stockholm were discharged from the hospital at times when no technical assistance for the performance of the intravenous glucose tolerance test (IVGTT) was available 2 female patients did not want to participate and 2 male and 1 female patient were omitted by mistake

There were *150 men* mean age 60 range 39 to 80 years and *40 women* mean age 66 range 51 to 81 years These ages as subsequently denote the ages of the subjects at the time of their first IVGTT

The *diagnosis* of myocardial infarction was based on the coexistence of at least 2 of the 3 following criteria a typical history transaminase (GOT GPT) elevations and ECG findings suggestive of acute myocardial infarction using as subsequently 16 leads (I II III aVR aVL aVF CR 1—2—4—5—7 V 1—2—4—5—7) The hospital records were available to me in all cases

The routine *treatment* of the patients during hospitalisation included oral anticoagulants and did not change essentially during the time of the present study

2 160 patients with *one or more myocardial infarctions* for which they had been hospitalised but whose first myocardial infarction had not been treated at the Seraphimer Hospital during the time of the present study 81 of these patients had been controlled and or treated some time in the Seraphimer Hospital for their ischaemic heart disease since the start of the present investigation and 79 patients had been referred to me for IVGTTs by colleagues at other hospitals These two groups did not differ significantly as to age the means being 58 and 56 years respectively All in all there were *144 men* mean age 57 range 33 to 76 years and *16 women* mean age 64 range 52 to 72 years 113 patients had survived one myocardial infarction and 47 patients two or more The time interval between a first myocardial in

by diabetic glucose tolerance only, might be related to ID as well as is overt diabetes Moreover, the association between carbohydrate metabolism and ID is only partly elucidated by limiting such investigations to overt diabetes These considerations motivated a study of glucose tolerance in seemingly nondiabetic patients with ID

Diabetes mellitus is a disease of unknown cause and nature As a working definition I have chosen the following Diabetes mellitus is a chronic disease characterised by low glucose tolerance, defined by oral or intravenous glucose tolerance tests in well nourished individuals on their ordinary weight maintaining diets under basal conditions — Several other disorders frequently run with low glucose tolerance such as chronic pancreatic disease acromegaly Cushing s disease, haemochromatosis phaeochromocytoma thyroid disease, malignant neoplastic or wasting conditions In these, on the other hand the low glucose tolerance is not a characteristic feature and may become normalised after correction of the underlying disorder At present it is uncertain whether the low glucose tolerance in these conditions should be regarded as equivalent to diabetes mellitus In want of better knowledge such patients have therefore been excluded from the present study

Glucose tolerance can be determined either by oral or intravenous loading The oral glucose tolerance test remains the most widely used, but still no generally accepted uniform criteria exist as to its performance or interpretation For the present study therefore a simple intravenous glucose tolerance test was chosen, the result of which is expressed as a k value representing the per cent per minute reduction of blood glucose

The present investigation was begun in November 1960, at which time the literature contained some information on oral glucose tolerance in non-diabetic patients with ID, but none on intravenous glucose tolerance in such patients In 1934 Edelmann presented a study of oral glucose tolerance in survivors from myocardial infarction and later reports appeared by Raab & Rabinowitz 1936 Goldenberg et al in 1945, by Bartels & Rullo in 1958, by Boehle & Schrade, and Waddell & Field in 1960 Since then studies have been published by Aleksandrow et al, Sowton and Wahlberg in 1962 by Tibblin & Cramer, Frehner & Wegman and Reaven et al in 1963 by Ryan et al, Nye, and Fabrykant & Gelfand in 1964, by Braunsteiner et al and Cohen & Shafrir in 1965 With the exception of the studies by Wahlberg Frehner & Wegman, and Ryan et al oral glucose tolerance tests were employed All studies but that of Ryan et al showed a high frequency of abnormal glucose tolerance tests but the interpretations of this finding have been diverging Most of these studies have dealt with small numbers of patients, who have been selected differently and several important problems as regards the relation between glucose tolerance and ID have not been elucidated

The aim of the present investigation was to study the intravenous glucose tolerance in patients with myocardial infarction angina pectoris and intermittent claudication in the absence of overt diabetes mellitus An attempt was also made to assess the influence of certain conditions on intravenous glucose tolerance, and its variation and prognostic significance were evaluated

thrombosis of the lower limbs 1 had par odontopathia and 1 subject had suffered a head injury There were 108 men, mean age 59 range 32 to 89 years and 92 women, mean age 55 range 34 to 82 years

C 80 patients with *clinical diabetes mellitus* All patients were controlled at the Medical Department of the Seraphimer Hospital 49 patients had recently diagnosed, untreated diabetes 21 patients had known diabetes of more than 6 months duration for which they had received no or only dietary treatment and 10 patients were receiving sulphonylurea treatment which in all cases had been withheld for at least 24 hours before any IVGTTs No significant age differences between these categories existed There were 55 men mean age 57, range 30 to 88 years and 25 females mean age 62 range 41 to 84 years

Diabetes mellitus was *diagnosed* by repeated findings of glucosuria and fasting blood glucose exceeding 110 mg per 100 ml the two conditions not necessarily coexisting

Principles for selection

A 1 These patients were selected because they had survived the time of hospitalisation for their first acute myocardial infarction

A 2—4 Of this heterogeneous group of 340 patients the 220 who had been controlled or treated at the Seraphimer Hospital were selected by myself primarily as they had ID Of the remaining 120 patients referred to me by colleagues for IVGTTs some were selected because of known additional hyperlipemia Otherwise the principles for selection apart from the presence of ID were not known to me

B These subjects were selected primarily as they had no signs of cardiovascular disease according to the above In many cases they were also selected because of age diabetic heredity obesity and hypertension in order to evaluate the influence of these factors in intravenous glucose tolerance

C These patients were selected by the presence of clinical diabetes not treated with insulin and by ages similar to those under A

General characteristics of the material

With the exception of the diabetics no one had had glucosuria under basal conditions nor a history or signs suggestive of clinical diabetes endocrine or metabolic disease prior to the study Nor did anyone show evidence of hepatic or pancreatic dysfunction renal failure malignant neoplastic disease mental deterioration nor of rheumatic valvular or congenital heart disease

All participants were in good general condition at the time of the tests With the exception of some patients under A 1 who will be accounted for in the following all were ambulant although hospitalised in many cases No special preparatory diets were given which is further commented on under Methods

farction and a first IVGTT varied from 6 weeks to 17 years

Myocardial infarction was *diagnosed* as under A 1 when possible, and was considered to have occurred if so stated in available hospital records or by the referring colleagues in the remaining cases

3 120 patients with *angina pectoris* but without a history or ECG findings suggestive of a previous myocardial infarction 88 of the patients had been controlled and/or treated for their ischaemic heart disease some time at the Seraphimer Hospital since the start of the present study, and the remaining 32 patients were referred to me for IVGTTs by colleagues at other hospitals The two groups did not differ significantly as regards ages, the mean being 58 years for both There were *94 men*, mean age 57, range 36 to 85 years, and *26 women*, mean age 58, range 43 to 80 years The duration of their disease prior to the first IVGTT varied from 6 months to 16 years

Angina pectoris was *diagnosed* by a typical history of oppressive and/or painful substernal sensations with or without radiation provoked and reproducible by physical effort, and relieved within 10 minutes by rest and/or nitrites

4 60 patients with *intermittent claudication* but without a history of ischaemic heart disease or ECG findings suggestive of an earlier myocardial infarction 42 of the patients had been treated and/or controlled for their ischaemic disease some time at the Seraphimer Hospital since the start of the present study, and the remaining 18 patients had been referred to me for IVGTTs by colleagues at other hospitals The two groups did not differ significantly as to age the means being 61 and 59 years respectively There were *50 men*, mean age 60 range 39 to 77 years, and *10 women*, mean age 59, range 40 to 72 years The duration of their disease prior to the first IVGTT varied from 3 months to 14 years

Intermittent claudication was *diagnosed* by a typical history of pain in the calves provoked and reproducible by walking and/or running, and relieved by rest within 10 minutes Oscillometry of the legs was routinely undertaken and in all these instances abnormally weak arterial pulsations were recorded from the affected limbs No cases of suspected or verified Buerger's disease were included, nor any in whom embolic incidents were considered to be the cause of the symptoms

B 200 subjects without a history or physical signs of cardiovascular disease and with a normal ECG at rest, using the above given 16 leads These subjects will be referred to as *controls* in the following 170 of them were treated or controlled at either the medical or surgical departments of the Seraphimer Hospital as outpatients or inpatients for non debilitating disorders at the time of their first IVGTTs, and the remaining 30 subjects had volunteered for the test 55 subjects were considered healthy and had either volunteered for the test or had it performed as a part of a health control or other somatic investigation, 30 subjects had some gastro-intestinal disorder, 29 subjects had asymptomatic obesity or hypertension, 16 subjects had xanthomatosis or known hyperlipemia 15 subjects had disorders of the musculo skeletal system 15 subjects were surgical outpatients with minor disorders 14 subjects had symptoms considered to be of neurotic origin 10 subjects had had infections of the respiratory or urinary tracts 8 subjects were anemic 4 subjects had neurological disorders 2 subjects had venous

Marks (1959) from capillary blood samples from the earlobes The linear function of glucose concentration and photometric extinction within the range 0 to 400 mg per 100 ml for the latter method was tested at least twice yearly Triplicate standards of at least two different concentrations were run with the unknown samples each day The methodological error (S D $_d$ $\sqrt{2}$) for a single blood glucose determination calculated from 250 randomly selected duplicate fasting capillary blood samples was 1 5 mg per 100 ml The blood sampling and the determination of glucose values were in all instances carried out by a specially assign d technician

Expression of the result of the intravenous glucose tolerance test (IVGTT) During the hyperglycemia approximately between 20 and 60 minutes after the end of the glucose injection the formation of the logarithms of the blood glucose values suggests a straight line when plotted against time as was originally described by Hamilton & Stein (1942) Hence glucose utilisation during the hyperglycemic phase appears to be proportional to blood glucose concentration i e follows the order of a monomolecular reaction which is expressed by the formula $BG(t) = BG(o)\ e^{-kt}$ where BG(t) is the blood glucose concentration at any time t and BG(o) the blood glucose concentration at time zero e the basis for the natural logarithms and k the disappearance rate constant for glucose from the blood For detailed explanations see Conard (1955) Ikkos & Luft (1957) and Lundbaek (1964) The half life of blood glucose can be determined graphically by extrapolation of the straight line formed by the logarithms of the glucose values and the glucose utilisation can then be expressed as a k value representing the disappearance of blood glucose in per cent per minute according to the formula 0 693 100 $t_{\frac{1}{2}}$ which is derived from the above formula For practical reasons semilogarithmic graphpapers were used on which the absolute blood glucose values were plotted see fig 1

In this study glucose utilisation was calculated from the blood glucose values within the 20 to 60 minutes interval with the exclusion of values 10 mg per 100 ml and less above the fasting level, as there often is a deviation from the linearity formed by the glucose values around these levels

The *methodological error* involved in determining k values graphically was studied as follows The author and two co-workers referred to as observers A B and C in table 1 independently estimated the k values from 30 randomly selected tests given in different sequences in 2 separate runs referred to as I and II in the table New plots and graphpapers were used for each estimation Paired differences for the k values of each test could then be obtained and the methodological error of a single k value determination (S D $_d$ $\sqrt{2}$) was calculated for each observer separately and for randomly selected comparisons between the observers In no instances were significant differences obtained The intra individual methodological error for each observer was 0 01 which was somewhat smaller than the differences obtained on inter individual comparisons i e 0 02 and 0 03

The k value might be dependent on different methods for blood glucose determination or blood sampling but when comparing the results from other studies these factors seem to be without importance According to my own experience the methods of Hagedorn Jensen and of Marks yield

METHODS

Definitions

Diabetic heredity was considered present in participants with knowledge of diabetes occurring in any of the grandparents or their siblings parents or their siblings, or own siblings

Hypertension was defined as repeated recordings of the diastolic blood pressure exceeding 100 mm of mercury or a clinical history of high blood pressure for which pharmacological treatment had been given

Obesity was defined as 10 per cent or more overweight according to the height and weight tables of the Danish life insurance company Hafnia as presented by K arup (1956)

Statistical methods

Statistical analysis was routinely performed with Wilcoxon s rank sample tests for paired and unpaired samples the chi square test or Spearman s rank correlation test (Documenta Geigy, Scientific tables 1960) The normality of distributions of values was tested according to methods presented by Snedecor (1956) Probability levels (P) higher than 5 per cent were considered to be without significance

The intravenous glucose tolerance test

Preparation of participants Hospitalised patients have routinely been on the ordinary hospital diet which supplies around 200 g of carbohydrates and 2200 calories daily Exceptions were made for diabetics and for patients on weight reducing regimens No supervision of the actual food intake during the days before the test occurred

Non hospitalised participants were routinely asked to follow their ordinary diets the days before the test to avoid any kind of caloric or carbohydrate restriction and were especially told not to refrain from their ordinary bread and potato intake From routine inquiries, daily carbohydrate intakes estimated to be lower than 100 g were not met with

The participants were asked not to eat nor to take any drugs after 8 00 p m preceeding the test, but they were allowed to drink water The tests were started between 8 00 and 10 00 a m All were reclining for at least 15 minutes before the start of the tests

Procedure After taking duplicate or triplicate fasting capillary blood samples for glucose determination 25 g of glucose in a 50 or 60 per cent aqueous solution were injected intravenously in 2 to 4 minutes Zero time was set at the end of the injection Blood samples were then taken at 10 and 20 minutes, and from then on every 5th minute until 60 minutes the samples at 20 and 60 minutes being in duplicate The participants were kept lying still throughout the tests

In the first 52 patients of the present study blood sugar levels were estimated by the Hagedorn Jensen (1935) method from capillary blood samples from the fingertips Thereafter *blood glucose* levels were determined enzymatically according to

Marks (1959) from capillary blood samples from the earlobes The linear function of glucose concentration and photometric extinction within the range 0 to 400 mg per 100 ml for the latter method was tested at least twice yearly Triplicate standards of at least two different concentrations were run with the unknown samples each day The methodological error (S D $d\sqrt{2}$) for a single blood glucose determination calculated from 250 randomly selected duplicate fasting capillary blood samples was 1 5 mg per 100 ml The blood sampling and the determination of glucose values were in all instances carried out by a specially assigned technician

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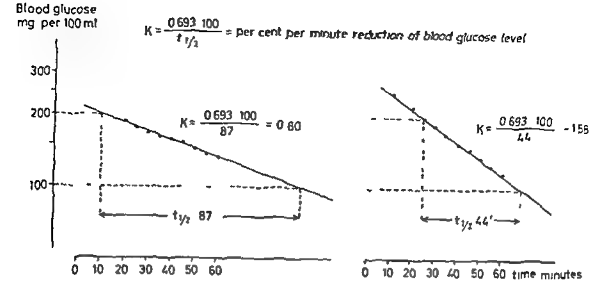


Fig 1 Calculation of k values

the same results as regards the intravenous glucose tolerance (IVGT) 23 participants were tested by both methods on different occasions but under comparable conditions The mean k values were 1.01 in both instances, the distributions being of no significant difference

The linearity of the time function of the logarithms of the absolute blood glucose values after intravenous glucose loading has been questioned (Greville 1943, Amatuzio et el 1953, Hlad & Elrick 1959) A corresponding linear function has instead been claimed by the above authors for different kinds of excess blood glucose values (absolute minus fasting values absolute minus limiting values) wherefore the following study was undertaken

	Mean k I	Mean k II	Mean k-difference ± S D (Methodological error=S D $\sqrt{2}$)		
Observer A	1.14	1.14	AI-AII 0.00±0.02 (0.01)	AI-BII 0.00±0.03 (0.02)	AII-CI 0.00±0.05 (0.03)
Observer B	1.13	1.14	BI-BII 0.00±0.02 (0.01)	BI-AII 0.00±0.03 (0.02)	BI-CI 0.01±0.04 (0.03)
Observer C	1.15	1.14	CI-CII 0.00±0.02 (0.01)	CII-AI 0.00±0.04 (0.03)	CI-BII 0.00±0.04 (0.03)

Table 1 Comparison of the k values obtained by 3 observers from the results of 30 intravenous glucose tolerance tests given twice in different sequences I and II

Blood glucose mg per 100 ml	Log equation for 300 IVGTTs y 2 4082 ~ 0 004530 X							
Mean observ ed	210	197	187	177	168	160	152	145	137
Mean calculated	208	197	187	178	169	160	152	144	137
Mean difference SD	2 3	0+3	0 2	1 3	1 3	0 2	0 3	1 2	0 2

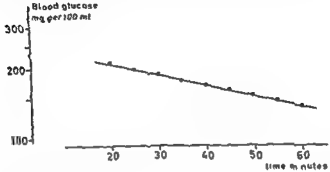


Fig 2 The mean regression line and its log equation for 300 intravenous glucose tolerance tests the mean observed and calculated blood glucose values the mean *differences and the S.D of the dif ferences* at each observation time

Three hundred tests were randomly select ed from my material in which all blood glucose observations during the 20 to 60 minutes interval exceeded the fasting level by more than 10 mg per 100 ml A computer (SAAB D 21) calculated the regression line and the differences between the observed and the calculated blood glucose values at each observation time for each of the 300 tests The means ± S D of these differences were also calculated and the results are shown in fig 2 where also the mean regression line for the 300 tests is drawn and its equation is given

It is seen that the formation of the mean observed blood glucose values around their regression line suggests linearity and that the *mean deviations from* the regression line are insignificant In most instances they do not exceed the width of an ordinary lead pencil line The standard deviations of the differences at each observation time are similar and so *small 2 to 3 mg* per 100 ml that they imply no inconveniences as regards the graphical estimation of *the k* value

The *linearity* of a regression function for a grouped sample can be tested by compar ing the variance of the column means around the regression line with the variance within the columns (Documenta Geigy 1960) The data needed for the analysis were calculated by a computer (IBM 70—90) The test quotient $s_2{}^2 / s_1{}^2$ *for the* 300 tests was 0 307 which means that the linearity of their regression function was not *disproved at the* 1 per cent level

In the present study the *glucose dose* was 25 g irrespective of body weight The litera ture provides few and somewhat contro versial data as to the effect of different glucose doses on the IVGT (Amatuzio et

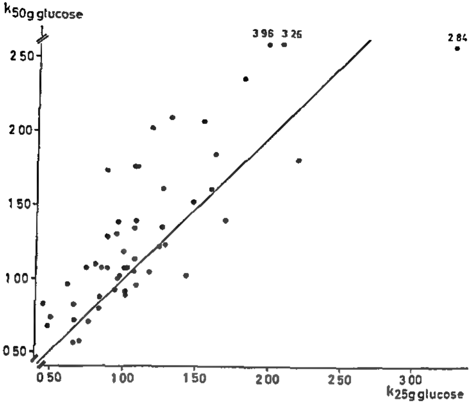


Fig 3 The k values of intravenous glucose tolerance tests using 25 and 50 g of glucose on separate occasions in 52 individuals

al 1953, Duncan 1956 Moorhouse et al 1963) To investigate this, the IVGT was tested with both 25 and 50 g of glucose on separate occasions in each of 52 individuals There were 42 men and 10 women, mean age 57, range 32 to 80 years 36 of them belonged to the patients under A, 11 to the subjects under B, and 5 to the diabetics under C The results are shown in fig 3 where the observations in each individual have been plotted in a coordinate system The time interval between any two tests was less than 6 months in 42 instances In 15 instances the higher glucose dose was given first 36 of them had higher k values after the higher glucose dose, the mean k value after the 25 g load being 1 12 as compared to 1 36 after the 50 g load ($P < 0\,001$) The exclusion of those in whom the interval between the tests exceeded 6 months did not affect the results essentially Each of the 5 diabetics had higher k values after the higher glucose dose and in one of them a borderline k value of 1 07 was obtained as compared to 0 84 on the lower glucose dose The increases of the k values after the 50 g load occurred along the whole range of k values obtained with the 25 g load The 10 numerically greatest k differences were also such increases and occurred in 2 individuals with diabetic in 2 with borderline and in 6 with normal k values after the 25 g glucose load

The variation of the k value after the two glucose doses occurred relatively independently of body weight as illustrated in fig 4 No rank correlation was

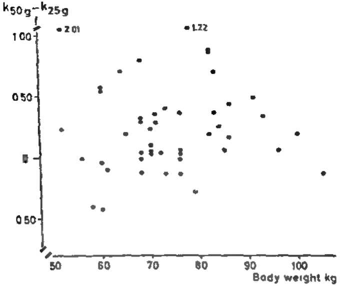


Fig 4 The relation between the body weight and the difference in the k values obtained at intravenous glucose tolerance tests using 25 and 50 g of glucose in 52 individuals

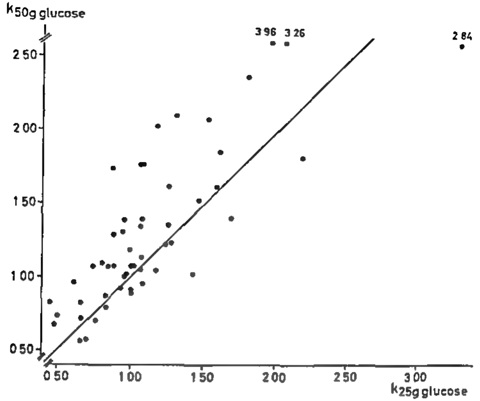
obtained between the change of the k value and body weight In spite of this the increase of the k value after the higher glucose dose was more regular in the 14 participants weighing more than 80 kg as 13 of them responded thus as compared o 22 out of the 38 lighter participants (0 02>P>0 01)

These findings imply a general increase of the k values with the use of a 50 g glucose dose but do not elucidate the effect on the k values of a body weight adjusted glucose dose Such an effect would be most pronounced in the extremes of the range of body weight Therefore pairs of individuals were selected matched according to sex age the occurrence of obesity and general condition but with a weight difference of at least 20 kg 38 pairs could thus be obtained 26 of them with ID under A and 12 from the controls under B 4 pairs were female and in 14 pairs both were obese The glucose dose was 25 g For the lighter individuals the mean age was 57 years the mean weight 65 kg, and the mean k value 1 16 Corresponding figures for the heavier individuals were 57 years 92 kg and the mean k value 1 19 the difference between the k values not being significant

Discussion

The effect of dietary abnormalities on glucose tolerance has long been recognised (Bernard 1846) of which the most important conditions are starvation and carbohydrate deprivation This has prompted several authors to stress the necessity of certain carbohydrate rich preparatory diets in order to avoid so called false diabetic results Such diets are still commonly used

In the often cited papers by Sweeney (1927) Himsworth (1934) and Conn (1940) short term starvation or diets free



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The variation of the k value after the two glucose doses occurred relatively independently of body weight as illustrated in fig 4 No rank correlation was

In the present study the half life of blood glucose following the glucose loading was estimated graphically from blood glucose values during the 20 to 60 minutes interval after the end of the injection with the exclusion of values 10 mg per 100 ml or less above the fasting level For some time after the glucose injection the disappearance of blood glucose is partly due to diffusion *into the glucose space and glucose values from this period should not be included in* the calculation of glucose utilisation The length of this period exhibits individual variation and from my experience it is over by 20 minutes after the glucose injection which is in accordance with the results obtained by Conard (1955) 15 minutes and Ikkos & Luft (1957) 25 minutes The above mentioned exclusion of glucose values less than 10 mg per 100 ml above the *fasting level was motivated as at these levels* the e may be a slowing of the disappearance rate of blood glucose with a subsequent digression from its linear function The methodological error involved in the graphical estimation of glucose half life was found to be negligible This is in accordance with the results of Conard (1955) who also showed that the k values thus obtained did not differ from those calculated mathematically

The literature is controversial as to what blood glucose values should form the basis for the calculation of the k value In 1942 Hamilton & Stein stated that the logarithms of blood sugar following glucose injection form a straight line for some time during the ensuing hyperglycemia This was denied by Greville in 1943 who suggested that at any instant the rate of fall in bloodsugar is proportional to the excess of the blood sugar value above the limiting value y_o the limiting value not being identical with the fasting value In 1953 Amatuzio et al *claimed that excess* blood glucose values representing the absolute minus the fasting values should instead be used for the calculation of k values, and in 1959 Hlad & Elrick proposed still another excess glucose value and a method for slope analysis for corresponding purposes Also from a clinical *point of view the equation for blood glucose disappearance as suggested by the latter* authors can be questioned They somewhat surprisingly arrived at that in a series of 17 patients with mild diabetes (unpublished data) we found that C_{eq} exceeded C_f in every case whereas k values were not significantly different from normal

On the other hand Ikkos & Luft (1957) in an extensive mathematical analysis of the problem, using the method of orthogonal polynomials found that in their own material of non diabetic subjects the decrease of the logarithms for the absolute blood glucose values had the characteristics of a straight line or a first order reaction from 25 to 30 minutes after the beginning of the glucose injection until 60 minutes *which was not the case when excess glucose* values according to Amatuzio et al were used correspondingly When they applied the same analytical method to the data from the tables of Amatuzio et al they obtained a linear function for the logarithms of the absolute glucose values 28 to 60 minutes after the injection, but also for the excess glucose values between 4 and 44 minutes When they correspondingly analysed the data for the diabetics of both studies they obtained more or less the same characteristics as regards the linearity of function for the decrease of the logarithms of both absolute and excess glucose values They

from carbohydrate or with a very low such content were found to produce diabetic oral glucose tolerance curves, which became normal after carbohydrate rich diets As the diabetic curves were produced under conditions when glucose tolerance tests are not performed for diagnostic purposes, or on diets not met with in ordinary life, these findings are of physiological rather than practical interest In 1954 Irving & Wang also questioned the use of preparatory diets when they found that 4 days of a diet containing 100 g of carbohydrate daily but otherwise unrestricted did not produce any diabetic curves nor did it produce lower glucose tolerance than diets containing 300 g of carbohydrate daily They concluded that there is no necessity for augmenting the normal diet of an adequately nourished patient before the performance of a glucose tolerance test In 1960 Wilkerson et al arrived at essentially the same results and conclusions in two separate studies and suggested that the routine of a high carbohydrate preparation for a glucose tolerance test has been exaggerated In the present study no participant has been encountered whose ordinary daily carbohydrate intake was estimated to be lower than 100 g Corresponding findings were made by Wilkerson et al (1960) who in a survey of 441 non diabetic persons in a hospital outpatient clinic found a daily intake of less than 100 g of carbohydrate in only 1 per cent

Against this background preparatory diets of a few days duration and with a carbohydrate intake of 200 to 300 g daily generally seem to be without importance for the results of glucose tolerance tests

Also glucose tolerance tests are generally used to detect diabetic states, and the idea of priming the participants with diets aiming at a temporary improvement of the glucose tolerance appears fundamentally wrong to me These procedures bring with them several practical disadvantages, and there is not always time to carry them out Many persons, especially the elderly find carbohydrate rich diets nauseating and upsetting their digestion, and as a close dietary supervision seldom can be achieved, it is uncertain how and how often given instructions are really followed In the present study, the dietary instructions given were only aimed at making sure that the participants really ate as usually before the test, and not on their own initiative restricted their habitual carbohydrate or caloric intake, which according to my experience occurs especially with obese persons

The above studies have all dealt with the influence of diet on oral glucose tolerance, and in want of information one has to assume that the results also apply to IVGT My experience concerning the effect of diet on IVGT is limited to the findings in 13 subjects most of them overweight who were on weight reducing regimens for more than one week and who were losing weight at the time of the test Their mean k value under these conditions was 0 88 and when they were retested under their ordinary conditions the mean k value was 1 33 (P<0 01) Their weights were essentially the same on both occasions

The routine duration of the fasting time for the participants varied from 12 to 16 hours This variation cannot have caused any systematic effect on the results as the starting times for the tests were randomly distributed Also, in 6 subjects who misunderstood given instructions and had no evening meal preceding the test, the prolonged fasting did not affect their IVGT

In the present study the half life of blood glucose following the glucose loading was estimated graphically from blood glucose values during the 20 to 60 minutes interval after the end of the injection with the exclusion of values 10 mg per 100 ml or less above the fasting level For some time after the glucose injection the disappearance of blood glucose is partly due to diffusion into the glucose space and glucose values from this period should not be included in the calculation of glucose utilisation The length of this period exhibits individual variation and from my experience it is over by 20 minutes after the glucose injection which is in accordance with the results obtained by Conard (1955) 15 minutes, and Ikkos & Luft (1957) 25 minutes The above mentioned exclusion of glucose values less than 10 mg per 100 ml above the fasting level was motivated as at these levels there may be a slowing of the disappearance rate of blood glucose with a subsequent digression from its linear function The methodological error involved in the graphical estimation of glucose half life was found to be negligible This is in accordance with the results of Conard (1955) who also showed that the k values thus obtained did not differ from those calculated mathematically

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concluded, that for the calculation of the true rate of disappearance of glucose, the absolute glucose values have to be used. Similar conclusions were drawn by West & Wood (1959) after analysis of their own data and those of others. The present study of the above discussed regression function for the logarithms of the absolute blood glucose values was based on data from 300 randomly selected tests and the mathematical analysis was performed with the method for grouped samples (Documenta Geigy 1960). Only a few tests from patients with clinical diabetes were included but there were many with diabetic or borderline IVGT, the mean k value being 1.05. The analysis did not disprove the linearity of the regression function ($P<0.01$).

The evidence presented for a linear regression function for the logarithms of the absolute blood glucose values during hyperglycemia does not disprove a corresponding linearity for excess glucose values under certain conditions, which was also found by Ikkos & Luft (1957). However as the absolute blood glucose values have been shown to constitute an adequate basis for the calculation of the k value for blood glucose disappearance and as the more complicated excess glucose values hardly can be claimed to describe the disposal of glucose more adequately, the use of the latter for this purpose seems rather meaningless.

The glucose dose in this study was 25 g irrespective of the participant's body weight, which is a commonly employed dosage (Amatuzio et al. 1953, Duncan 1956, Ikkos & Luft 1957, Lundbaek 1960). The effect of varying doses of glucose on the k value in man has attained relatively small attention and is often considered to be without importance. Using the absolute blood glucose values from the tables of Amatuzio et al. (1953) I could find no significant difference in the k values of 13 normal men after 25 g and 35 g of glucose, the mean k values being 1.36 and 1.47 respectively. Duncan (1956) used glucose doses of 25 and 50 g and obtained significantly higher k values on the higher dose in 8 normal men, the mean k values being 1.38 and 1.98 respectively, and in 6 mild diabetics the mean k values being 0.56 and 0.74 respectively. Moorhouse et al. (1963) found that increasing the glucose dose gave increasing k values in 13 normal subjects but not in 10 diabetics. According to my own results a 50 g glucose dose gives significantly higher k values than does a 25 g dose, but the increase was inconstant and occurred irrespectively of the glucose tolerance on the lower dose. Of the 5 patients with clinical diabetes all responded with higher k values on the higher glucose dose. No correlation was obtained between the body weight and the change in the k value, but the increase after the higher dose was more predictable in the heavier subjects. The k values after both doses were usually classified similarly according to the criteria set up for the 25 g dose. Only 2 subjects out of 17 with diabetic k values after 25 g of glucose had normal k values after 50 g. It seemed improbable that an adjustment of the glucose dose to body weight would result in k values essentially differing from those obtained with a uniform 25 g dose.

The oral glucose tolerance test (OGTT)

The OGTT was performed under the same conditions as the IVGTT. The oral glucose tolerance (OGT) was tested with 70 g of glucose dissolved in 300 cc of

water flavoured with lemon The ingestion of the glucose solution was completed within 5 minutes and zero time was set at the end of the ingestion Duplicate capillary blood samples for glucose determination were drawn from the earlobes in fasting and at 30 60 90 120 and 150 minutes

The insulin sensitivity test (IST)

The IST was performed under the same conditions as the IVGTT The insulin sensitivity (IS) was tested with crystalline insulin (Vitrum[R]) in a solution containing 5 IE per ml After taking duplicate or triplicate fasting capillary blood samples for glucose determination 0 05 IE of insulin per kg body weight were injected intra venously in 2 minutes Zero time was set at the end of the injection Duplicate capillary blood samples for glucose determination were taken every 10th minute until 60 minutes The IS was expressed as per cent decrease of fasting blood glucose

concluded that for the calculation of the true rate of disappearance of glucose, the absolute glucose values have to be used Similar conclusions were drawn by West & Wood (1959) after analysis of their own data and those of others The present study of the above discussed regression function for the logarithms of the absolute blood glucose values was based on data from 300 randomly selected tests and the mathematical analysis was performed with the method for grouped samples (Documenta Geigy 1960) Only a few tests from patients with clinical diabetes were included but there were many with diabetic or borderline IVGT the mean k value being 1 05 The analysis did not disprove the linearity of the regression function ($P<0\ 01$)

The evidence presented for a linear regression function for the logarithms of the absolute blood glucose values during hyperglycemia does not disprove a corresponding linearity for excess glucose values under certain conditions which was also found by Ikkos & Luft (1957) However as the absolute blood glucose values have been shown to constitute an adequate basis for the calculation of the k value for blood glucose disappearance and as the more complicated excess glucose values hardly can be claimed to describe the disposal of glucose more adequately, the use of the latter for this purpose seems rather meaningless

The glucose dose in this study was 25 g irrespective of the participant s body weight which is a commonly employed dosage (Amatuzio et al 1953, Duncan 1956 Ikkos & Luft 1957, Lundbaek 1960) The effect of varying doses of glucose on the k value in man has attained relatively small attention and is often considered to be without importance Using the absolute blood glucose values from the tables of Amatuzio et al (1953) I could find no significant difference in the k values of 13 normal men after 25 g and 35 g of glucose the mean k values being 1 36 and 1 47 respectively Duncan (1956) used glucose doses of 25 and 50 g and obtained significantly higher k values on the higher dose in 8 normal men the mean k values being 1 38 and 1 98 respectively and in 6 mild diabetics , the mean k values being 0 56 and 0 74 respectively Moorhouse et al (1963) found that increasing the glucose dose gave increasing k values in 13 normal subjects but not in 10 diabetics According to my own results a 50 g glucose dose gives significantly higher k values than does a 25 g dose but the increase was inconstant and occurred irrespectively of the glucose tolerance on the lower dose Of the 5 patients with clinical diabetes all responded with higher k values on the higher glucose dose No correlation was obtained between the body weight and the change in the k value but the increase after the higher dose was more predictable in the heavier subjects The k values after both doses were usually classified similarly according to the criteria set up for the 25 g dose Only 2 subjects out of 17 with diabetic k values after 25 g of glucose had normal k values after 50 g It seemed improbable that an adjustment of the glucose dose to body weight would result in k values essentially differing from those obtained with a uniform 25 g dose

The oral glucose tolerance test (OGTT)

The OGTT was performed under the same conditions as the IVGTT The oral glucose tolerance (OGT) was tested with 70 g of glucose dissolved in 300 cc of

water flavoured with lemon The ingestion of the glucose solution was completed within 5 minutes and zero time was set at the end of the ingestion Duplicate capillary blood samples for glucose determination were drawn from the earlobes in fasting and at 30 60 90 120 and 150 minutes

The insulin sensitivity test (IST)

The IST was performed under the same conditions as the IVGTT The insulin sensitivity (IS) was tested with crystalline insulin (Vitrum®) in a solution containing 5 IE per ml After taking duplicate or triplicate fasting capillary blood samples for glucose determination, 0 05 IE of insulin per kg body weight were injected intra venously in 2 minutes Zero time was set at the end of the injection Duplicate capillary blood samples for glucose determination were taken every 10th minute until 60 minutes The IS was expressed as per cent decrease of fasting blood glucose

IV

INTRAVENOUS GLUCOSE TOLERANCE IN CLINICAL DIABETES MELLITU

Introduction

In 1953 *Amatuzio* et al suggested the use of k values calculated from the excess blood glucose values obtained after intra venous glucose loading as a means of dis tinguishing diabetics from non diabetics Their study included 26 patients with known, mild diabetes controlled by diet alone (the majority had normal fasting blood sugars) and 13 patients with severe diabetes mellitus Diabetes mellitus had been diagnos ed in these patients by clinical evaluation and the 100 g standard oral glucose test From their tables the absolute blood glu cose values and corresponding k values were calculated by myself, according to which the mean k value was 0 51, the values rang ing from 0 00 to 1 26 The fasting blood glucose values ranged from 80 to 322 mg per 100 ml

Several papers have appeared later con ce ning intravenous glucose tolerance (IVGT) in diabetics using absolute blood glucose values for the estimation of the k values In 1955 Conard studied the IVGT of 90 diabetics 15 to 79 years old, whose diabetes had been recognised in the ordinary way (de façon formelle) by its clinical manifestations and the existence of glu cosuria To diminish the influence of renal factors on the IVGT the author had select ed patients with a moderate degree of fast ing hyperglycemia which in only two pa tients exceeded 200 mg per 100 ml Several patients treated with insulin we e included no exact data being given The mean k value was 0 54, the values ranging fro 0 10 to 0 99

In 1956 Duncan presented an investig tion of 21 patients suffering from mi diabetes mellitus, in whom the diagnosis h been firmly established on clinical grounds The ages ranged from 26 to 73 years, tl majority were controlled by diet alone, ar no one was obese According to his tab the mean k value was 0 66 the values ran ing from 0 43 to 1 01 The fasting bloc glucose values ranged from 105 to 280 m per 100 ml

In 1957 Ikkos & Luft published result from 22 intravenous glucose tolerance test (IVGTT) in 16 diabetics, some of whon were treated with insulin The mean k valu was 0 33 the values ranging from approxi mately 0 00 to 0 64 as estimated by mysel from the glucose values in the tables of the authors The fasting blood glucose values ranged from 76 to 412 mg per 100 ml

In 1959 Lundbaek reported on the IVGT of 60 diabetics 19 to 78 years old treated with insulin sulphonylurea and/or diet alone The mean k value was 0 63 the values ranging from 0 20 to 1 02 No information on the fasting blood glucose levels was given

In 1962 Creutzfeldt et al determined the IVGT of 20 latent or mild cases of adult diabetes without hepatic disease The mean k value was 0 68 the values ranging from 0 13 to 1 24 The mean fasting blood glu cose value was 116 mg per 100 ml

In 1964 Moorhouse et al presented data from 70 diabetics some of whom received

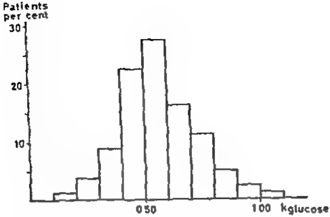

Fig 1 The distribution of the k values in 80 clinical diabetics

hypoglycemic agents such as insulin, sulphonylurea and phenformin . Diabetes was recognised by the presence of either a fasting blood glucose level of over 110 mg per 100 ml (Technicon autoanalyser) or of an abnormal glucose tolerance test . From their tables the mean k value was 0 50 the values ranging from 0 09 to 1 00 The fasting blood glucose values ranged from 81 to 108 mg per 100 ml 14 patients having values below 110 mg per 100 ml

The results of these studies differed to some extent especially as regards the highest k values which are of the greatest diagnostic importance These discrepancies may be due to different diagnostic criteria for diabetes mellitus and the heterogeneous selection of the patients

From the beginning of the present study k values 0 90 and lower were classified as diabetic k values 0 91 to 1 10 as borderline and k values 1 11 or higher as normal The word normal was chosen only for practical reasons to signify a range of k values not encountered in overt diabetes This classification was arbitrarily chosen on the basis of the results obtained by Conard (1955) and Lundbaek (1960) Their patients consisted of both juvenile and adult diabetics treated with insulin sulphonylurea, and or diet alone and it is not well known how such antidiabetic treatment or the duration of the disease in itself affects the IVGT The patients with ischaemic cardiovascular diseas (ID) of the present study had often received some other pharmacological or dietary treatment prior to their first IVGTTs Therefore it was considered of interest to investigate whether the chosen criteria for the classification of IVGT were valid if applied to a selection of adult clinical diabetics who were either untreated of who had received sulphonylurea and or diet only

Material See Chapter II

Methods See Chapter III

Results

The *distribution of the k values* obtained at the first IVGTT *in each of the* 80 patients is shown in *fig 1* The normality of the distribution was not disproved (P>

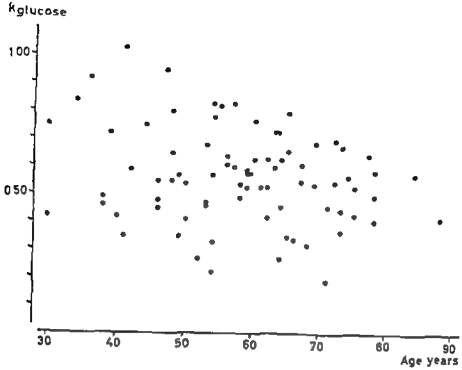

Fig 2 The relation between the k values and the ages of 80 clinical diabetics

0 05) The mean k value ± S D was 0 57 ± 0 17, the values ranging from 0 19 to 1 03 3 patients had k values 0 91 and higher

The *relation between the k values and the ages* at the time of the IVGTTs represented in fig 1 is illustrated in fig 2 No rank correlation was obtained on statistical analysis (R = 0 19 P>0 10)

There was no *influence of sex on the IVGT* The mean k values of the male and the female patients were 0 58 and 0 54 respectively the difference not being significant Nor was there any influence of *obesity* on the IVGT, as the k values of the 45 obese diabetics did not differ significantly from those of the 35 non obese their mean k values being 0 53 and 0 61 respectively

The mean k value of the 49 recently recognised diabetics was 0 57 as compared to 0 55 of the remaining ones the difference not being significant Their mean fasting blood glucose values were 154 and 146 mg per 100 ml respectively the difference not being significant

The *relation between the fasting blood glucose level and the k value* of the IVGTTs represented in fig 1 is illustrated in fig 3 A rank correlation was obtained between increasing fasting blood glucose levels and decreasing k values (R = —0 77 P<0 001) It is also seen that the patient with the highest k value 1 03 had a fasting blood glucose value of 80 mg per 100 ml In spite of this his diagnosis of diabetes was unquestionable according to above criteria and the values may have been due to treatment with sulphonylurea The mean fasting blood glucose value of the total number of patients was 151 mg per 100 ml the values ranging from 80 to 330 mg per 100 ml

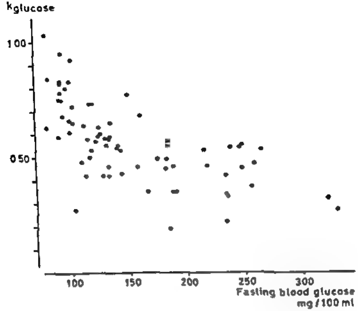

Fig 3 The relation between the fasting blood glucose levels and the k values of 80 clinical diabetics

Discussion

Diabetes mellitus is a chronic disease which is characterised by its low glucose tolerance An adequate definition of diabetic intravenous glucose tolerance should in my opinion be based on the results obtained in patients in whom it has been possible to make an unequivocal diagnosis of the disease without the aid of other glucose tolerance tests Thus for the present study only patients were included with clinical diabetes according to diagnostic criteria which I think can be generally accepted

The k values were normally distributed and the extreme values observed corresponded well with those to be expected statistically The range of the mean k value ± 2 S D was 0 23 to 0 91 and there occurred 2 lower (0 19 and 0 22) and 3 higher k values (0 92 0 95 and 1 03) Neither age obesity nor sex influenced the distribution of the k values As to the latter factor Moorhouse et al (1964) found the same for diabetics with fasting blood glucose levels under 200 mg per 100 ml above which they found a significantly higher mean k value for the women 0 30 as compared to 0 18 for the men In the present study the corresponding figures were 0 41 for both sexes

The k values of the previously untreated diabetics did not differ significantly from those of the patients who had received only dietary or sulphonylurea treatment neither did those of the two latter groups when compared correspondingly From these results nothing can be inferred about the influence of treatment or the duration of the disease on the IVGT in diabetes as the treated diabetics represented a selection in whom adequate chemical control of the disease was considered to be acquired with

Table 1 k values in diabetic patients

Author	n	k values		
		Mean	Range	≥0 91 *no*
Amatuzio et al *	39	0 53	*0 00—1 15*	5
Conard	90	0 54	0 10—0 99	3
Duncan*	21	0 66	0 43—1 01	1
Ikkos & Luft*	16	0 33	0 00—0 64	0
Lundbaek	60	0 63	0 20—1 02	6
Creutzfeldt et al	20	0 69	*0 13—1 24*	6
Moorhouse et al *	70	0 50	0 09—1 00	2
Wahlberg	80	0 57	0 10—1 03	3
Total	*396*	*0 56*	*0 00—1 24*	*26*

* The results were calculated by Wahlberg *from data in the tables of the authors*

the given treatment Jensen et al (1957) found that one and a half days of sulphonylurea treatment significantly ameliorated the IVGT in 21 diabetics : Corresponding results were obtained in the 11 diabetics of Baird & Duncan (1957), and Moorhouse et al (1964) arrived at similar results in [illegible] diabetics, in whom the last tablets were given 8 hours before the IVGTTs On the other hand Bastenie et al (1957) found no significant change of the IVGT in 18 diabetics after carbutamide treatment A remarkable improvement of the IVGT may appear initially in some diabetics after sulphonylurea treatment 2 patients of Jensen et al (1957) had k values around 1 60, and 2 patients of Bastenie et al (1957) had k values 1 9 after some days of treatment This improvement probably declines with time as no such values were met with in the studies reviewed below One of the patients of Bastenie et al (1957) was retested some months later and then had a k value of 0 6

A negative rank correlation between the fasting blood glucose level and the k value was obtained for the diabetics of the present study the function looking curvilinear Also in the studies of Amatuzio et al (1953), Duncan (1956) and Moorhouse et al (1964) similar correlations seem to be at hand In the latter study this correlation apparently occurred in the diabetics irrespectively of whether they were receiving hypoglycemic agents or not but no statistical analysis was given This correlation between the fasting blood glucose level and the k value must consequently affect the distribution of the k values in selections of diabetics Especially the crucial limiting higher k values will be rather dependent on chosen diagnostic criteria for diabetes mellitus This may explain the stray cases of Amatuzio et al (1953) with a fasting blood glucose value of 80 mg per 100 ml and a k value of 1 15 and of Creutzfeldt et al (1962) with a k value of 1 24 However the fasting blood glucose levels are probably not

th only factor determining the range of k values in diabetics. The fasting blood glucose values of Conard's (1955) patients were considerably lower than those in the diabetics of Moorhouse et al. (1964) or than those in the diabetics of the present study although the ranges of the k values were the same.

Although the criteria for diabetes and the selections of the patients differed, the above presented studies displayed similar ranges of k values, as summarised in table 1. Of the 396 patients in the table 26 or 7 per cent had k values 0.91 and higher. This motivates the use of 0.90 as the upper limit of diabetic k values, although a somewhat higher value could have been accepted statistically. As k values 0.91 to 1.10 are met with infrequently in patients diagnosed as diabetics their designation as borderline is useful. k values 1.11 and higher can be regarded as normal in the sense of being non diabetic, as only 2 patients from table 1, or 0.5 per cent, had such values.

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Duncan*	21	0 66	0 45—1 01	1
Ikkos & Luft*	16	0 33	0 00—0 64	0
Lundbaek	60	0 63	0 20—1 02	6
Creutzfeldt et al	20	0 69	0 13—1 24	6
Moorhouse et al *	70	0 50	0 09—1 00	2
Wahlberg	80	0 57	0 10—1 03	3
Total	396	0 56	0 00—1 24	26

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V

INTRAVENOUS GLUCOSE TOLERANCE IN SUBJECTS WITHOUT CLINICAL SIGNS OF CARDIOVASCULAR DISEASE

Introduction

Intravenous glucose tolerance (IVGT) has been studied in nondiabetic subjects since the beginning of the 20th century, and in 1940 Tunbridge & Allibone made an extensive review of the literature In 1942 Hamilton & Stein introduced the k value as a means of expressing IVGT, but since then there has unfortunately been no unanimity as regards what k values should be used, if they should be used or how the intravenous glucose tolerance test (IVGTT) should be performed

A study of the IVGT in subjects without clinical signs of cardiovascular disease or diabetes mellitus who also will be referred to as controls was undertaken to provide a background for some of the results obtained in seemingly nondiabetic patients with ischaemic cardiovascular disease (ID) Directly corresponding studies for comparison are not available Of authors using similar or the same IVGTT as that of the present study only Silverstone et al (1957) specified that their subjects had no cardiac disease Otherwise the subjects have been referred to as either nondiabetic, normal or healthy or have had a diagnosis not indicating cardiovascular disease A discussion of the results will be given below

Results

The distribution of the k values obtained at the first IVGTT in each patient is shown in fig 1 Their distribution appears skew and normality was rejected ($P<0\ 001$) The mean k value was 1 53, the values ranging from 0 66 to 3 85 The median k value was 1 42 4 per cent of the k values were diabetic, 10 per cent borderline and 86 per cent normal

The relation between the k values and the ages at the time of the IVGTTs represented in fig 1 is illustrated in fig 2 On statistical analysis a rank correlation was obtained ($R = -0\ 29$ $P<0\ 001$) between increasing age and decreasing k value This correlation was dependent on the results in the subjects 70 to 89 years old without whom it disappears As is further shown in fig 3 the decrease in IVGT with increasing age was due to a relative scarcity of high normal k values in these elderly subjects not to an increase in the frequency of diabetic k values The distribution of the k values in this age group differed both from that of the subjects 30 to 49 years of age and from that of the subjects 50 to 69 years of age ($P<0\ 001$ in both instances) whereas the latter groups did not differ significantly in this respect On the other hand the frequencies of diabetic borderline and normal k values in these three age groups did not differ significantly

The influence of *sex diabetic heredity obesity and hypertension* on the IVGT is shown in table 1 The males and the females did not differ significantly as regards their IVGT Neither did in this respect the subjects with diabetic heredity differ from

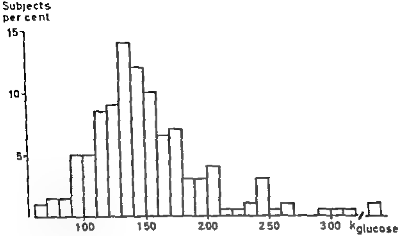

Fig 1 The per cent distribution of the k values in 203 subjects without clinical signs of cardiovascular disease

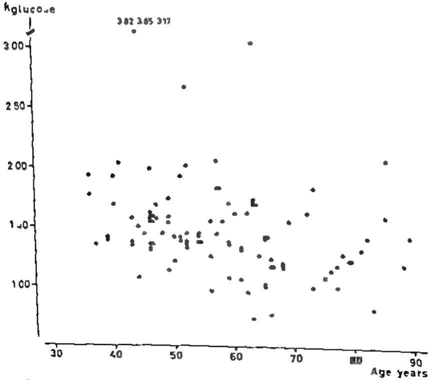

Fig The relation of k values to ages in 200 subjects without clinical signs of cardiovascular disease

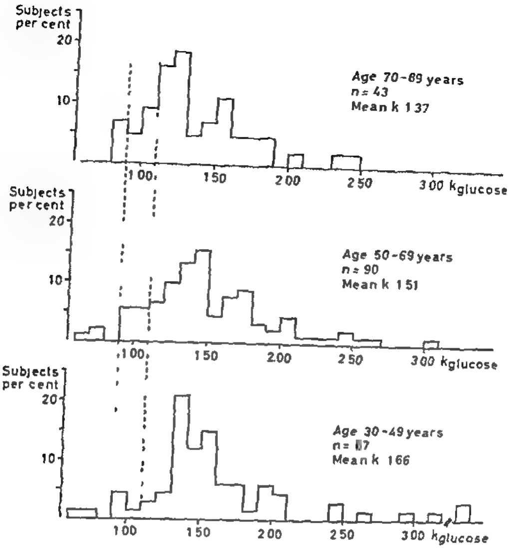

Fig 3 The per cent distributions of the k values in different age groups of subjects without clinical signs of cardiovascular disease

those without the obese subjects differ from the non obese nor the subjects with hyper tension from those without The k values of the 112 subjects with neither diabetic heredity obesity nor hypertension did not differ significantly from those of the 88 subjects with one or more of these features the means being 1 59 and 1 45 respectively 25 subjects had combinations of diabetic heredity, obesity and hypertension the mean k *value being* 1 42 Their k values did *not differ significantly from those of the subjects with only one of these features nor* from those of the subjects without any of them 82 subjects were and 118 were not hospitalised at the time of the test The k values of these two groups were of no significant difference the means being 1 62 and 1 46 respectively

The *relation between the fasting blood glucose levels and the k values* from the tests represented in fig 1 is illustrated in

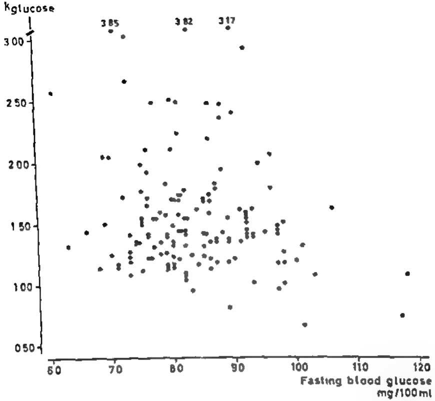

Fig 4 The relation of fasting blood glucose levels to k values in 200 subjects without clinical signs of cardiovascular disease

Table 1 The influence of sex diabetic heredity obesity and hypertension in 200 subjects without clinical signs of cardiovascular disease

	n	IVGT per cent			Mean K value	Mean age years
		Diabetic	Borderline	Normal		
Males	108	6	12	82	1.48	59
Females	92	1	7	92	1.58	55
Diabetic heredity	37	3	22	75	1.38	55
Obesity	56	9	14	77	1.46	58
Hypertension	24	4	17	79	1.45	53
Absence of diabetic heredity obesity hypertension	11	5	3	92	1.59	58
Total	200	4	10	86	1.53	57

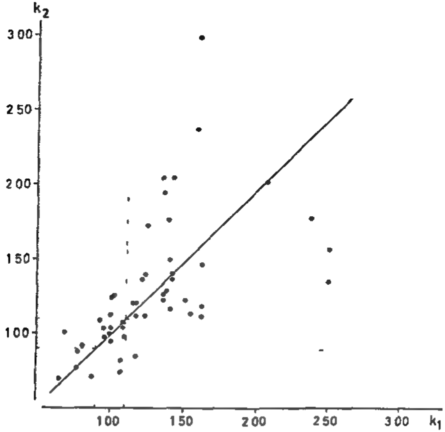

Fig 5 The relation of the results of repeated intravenous glucose tolerance tests k_1 and k in 50 subjects without clinical signs of cardiovascular disease

fig 4 A negative rank correlation was obtained ($R = -0\ 12$ $P<0\ 05$) The mean fasting blood glucose value was 83 mg per 100 ml range 60 to 118

50 subjects were *retested* at least once under comparable conditions and the results are shown in fig 5 In those retested more than once the first test was compared with the last one The mean interval between two tests was 18 months No systematic follow up was undertaken and the subjects were selected mostly on account of availability Special care was taken to retest the 28 subjects with initially diabetic or borderline IVGT, and this was carried out in 20 of them The k values obtained at the first and the last tests did not differ significantly the means being 1 27 and 1 28 respectively In 25 subjects the interval between two tests ranged from 24 to 48 months On separate comparison of these k values no significant difference was obtained the means being 1 38 and 1 37 respectively Changes as to the classification of the IVGT occurred in 2 subjects with initially diabetic IVGT who had become borderline in 5 subjects with initially borderline IVGT of whom 3 had become normal and 2 diabetic and in 1 subject with initially normal IVGT who had become diabetic The individual variation in IVGT appears considerable numerically but is

Table 2 The intravenous glucose tolerance of non-diabetic subjects

Author	n	k values		per cent		
		Mean	Range	Diabetic	Borderline	Normal
Amatuzio et al *	70	1.33	0.88—2.31	1	9	90
Conard	75	1.74	1.07—2.79	0	1	99
Duncan	8	1.37	1.01—1.89	0	7	93
Ikkos & Luft*	47	1.44	0.55—3.26	4	2	94
Silverstone et al	35	1.37	0.67—3.44	0	11	69
Creutzfeldt et al	15	1.47	1.11—2.04	0	0	100
Moorhouse et al *	33	1.61	0.74—2.76	6	15	79
Lundbaek	140	1.64	0.60—3.50	7	16	77
TOTAL	443	1.54	0.55—3.50	5	9	86
Wahlberg	200	1.53	0.66—3.85	4	10	86

* The results were calculated by Wahlberg from data in the tables of the authors

mostly pronounced within the normal range of k values and is of small practical importance

No subject had developed signs of cardiovascular disease at the time of any retest

Clinical diabetes mellitus is known to have developed in 1 obese male patient without diabetic heredity His first k value was 0.85 after some days of caloric restriction wherefore this has not been accounted for previously 18 months later on his normal unrestricted diet he had a fasting blood glucose value of 117 mg per 100 ml a k value of 0.73 but no symptoms of clinical diabetes This developed 6 months thereafter with subjective symptoms fasting hyperglycemia and glucosuria His weight had remained constant during the period of observation

Discussion

In the present investigation of IVGT in subjects without clinical signs of cardiovascular disease 4 per cent had diabetic, 10 per cent borderline and 86 per cent normal k values These results have been compared to those obtained in other selections of subjects without clinical diabetes as shown in table 2 As the compositions of these selections varied considerably a short presentation of them is given below

Amatuzio et al (1953) Healthy men ranging in age from 25 to 50 years with no family history of diabetes mellitus

Conard (1955) Individuals without disturbances of carbohydrate metabolism hepatic disease or obesity

Duncan (1956) Normal persons 5 females and 23 males 20 to 60 years of age nonobese with no family history of diabetes

mellitus and free from disease known to be associated with a disturbance in glucose tolerance

Silverstone et al (1957) Male subjects, 23 to 86 years of age, with no history or evidence of diabetes, hepatic disease, or cardiac decompensation or edema

Ikkos & Luft (1957) Healthy subjects and patients with a primary diagnosis other than diabetes mellitus

Creutzfeldt et al (1962) Individuals without metabolic disturbances or hepatic disease 20 to 60 years of age

Moorhouse et al (1964) Healthy men and women, 20 to 34 years of age

Lundbaek (1964) Patients with arthrosis, fibrositis, and neurosis, without symptoms of diabetes and without glucosuria ages from under 50 to above 70 years

In spite of the varying selections of subjects in these studies the results as regards their IVGT showed small variations The frequencies of diabetic, borderline, and normal k values in the present study and in the other added studies were almost identical, which was also true for the ranges of the k values and their means In none of these studies a diagnosis indicating cardiovascular disease was mentioned nor should the known occurrence of said disease be compatible with designations such as healthy or normal to the subjects Therefore it seems probable that under corresponding conditions the IVGT of subjects without signs of cardiovascular disease is diabetic in approximately 5 per cent, borderline in 10 per cent and normal in 85 per cent

Glucose tolerance decreases with age according to several investigations which was also the case in the present one In 1949 Smith & Shock and in 1952 Schneeberg & Finestone found that the lowering of blood sugar following a single intravenous glucose load was slower with increasing age Silverstone et al (1957) obtained lower k values for their older subjects as compared to their younger subjects, and similar results were arrived at by Lundbaek (1964) Employing oral glucose tolerance tests (OGTT) Short & Johnson (1938) in 132 normal weight and 409 overweight nondiabetic subjects found no decrease in the oral glucose tolerance (OGT) of either category below age 60 above which there was a slight decrease in the nonobese, and a marked decrease in the obese No statistical analysis was presented A decrease of the OGT by age was not found in the 50 subjects of Mosenthal & Barry (1950), nor in the 152 food handlers with negative screening tests for diabetes of Unger (1957) On the other hand a decrease of the OGT by age was found in a sample of subjects without glucosuria from the Birmingham, England, survey (1963) and in the surveys from Kristianstad, Sweden (1964), and from Tecumseh U S A (1965)

In the present study there was no significant difference in the IVGT of the subjects in the two age groups below age 70 but both groups differed in this respect from the subjects aged 70 or more Of particular interest is that these differences were not the result of an increase in the frequencies of diabetic and borderline k values among the elderly subjects which seems to be in accordance with the findings of Lundbaek (1964) The scatter diagram in chart 1 of Short & Johnson (1938) also corresponds remarkably well to that in fig 2 of the present study in which a correlation is difficult to detect It appears from the latter and the present studies that the association

between decreasing glucose tolerance and increasing age is weak and of small clinical importance

Moorhouse et al (1964) found significantly higher k values in healthy females than in healthy males the means being 1 86 and 1 47 repectively Lundbaek (1964) obtained similar results in his subjects age 70 and below but gave no statistical analysis In the present study no influence of sex on the IVGT was found

Diabetic heredity implies an increased risk of developing diabetes mellitus but its influence on glucose tolerance in seemingly nondiabetic adults is difficult to assess from the literature The risk of developing diabetes also increases with increasing age The clinical onset of the disease is generally not sudden in adults and must be preceded by a certain period of low glucose tolerance Therefore an association between diabetic heredity and low glucose tolerance could be expected In 1921 Sherrill obtained 21 abnormal OGTTs in 40 supposedly nondiabetic relatives of known diabetics On the other hand he also found impaired OGT in 13 subjects with a negative family history of diabetes and normal OGT in 16 other subjects

Tyner (1933) obtained no association between diabetic heredity and glucose tolerance in 1000 selected subjects 500 of whom with prediabetic and 500 with normal OGT Pincus & White (1934) obtained supernormal bloodsugar values at OGTTs in 25 per cent of their subjects with diabetic heredity and in 2 per cent of their controls but Lambert et al (1961) found no difference in the OGT of their subjects with and without diabetic heredity Nor did Nilsson (1962) find an association between IVGT and diabetic heredity in 18 year old conscripts using the same IVGTT as that in the present study which also failed to show such an association The lack of evidence for an influence of diabetic heredity on glucose tolerance in the above studies does not exclude its existence and may be due to the selections and the small numbers of subjects studied

It appears to be well established that the development of diabetes mellitus in adults is related to obesity but the influence of obesity on carbohydrate metabolism in non diabetic persons is less clear

High frequencies of abnormal responses to OGTTs in apparently nondiabetic persons were reported by Paullin & Sauls (1922) and Ogilvie (1935) but they tested no controls John (1929) found a higher prevalence of diabetic OGTTs in his obese subjects than in the non obese but the latter were not referred to as a control group by the author who does not compare the groups In 1933 Tyner found the same incidence of obesity in his 500 subjects with normal OGT as in his 500 subjects with prediabetic OGT but Short & Johnson (1938) found that there was an unmistakable correlation between the degrees of overweight and the incidence of impaired glucose tolerance irrespective of age In the papers by Newburgh & Conn (1939) and Newburgh (1942) obese adult diabetics acted as their own controls According to the latter paper 77 per cent of 47 patients achieved normal OGTTs after weight reduction of varying amounts In 1947 Ray found that in 110 obese office cases the glucose tolerance was normal in only 19 per cent of the women and 26 per cent of the men On the other hand, Unger (1957) found no influence of obesity on the OGT in 152 foodhandlers whereas

Morse et al (1960) obtained lower OGT and IVGT (if k values are calculated from the absolute blood glucose values in their tables) in 11 obese women than in controls Finally, in the Kristianstad survey (1964) there occurred a positive correlation between bodyfat and blood sugar level after ingestion of glucose in men aged 40—59 and 60—79 and in women aged 40—59 In the younger men and older women no such tendency was found, while among younger women the correlation appeared to be negative

The findings in these reviewed studies have been conflicting and sometimes inconclusive as regards the association between obesity and oral glucose tolerance To some extent these discrepancies may have been due to different methods and criteria for the interpretation of the results, and to differences in the selections studied The present investigation of subjects without cardiovascular disease did not shown a relation between obesity and IVGT Comparisons with the above studies are difficult to make but a further discussion will be given in the next chapter

Hypertension was of no influence on the IVGT of the subjects in the present study Oral glucose tolerance in hypertension was investigated by O Hare (1920), Drazin (1953), and Nye (1964), but no control groups were included

In 1963 Frethem studied the relation of fasting blood glucose level to the oral glucose tolerance curve in 401 subjects in most of whom there was a suspicion of mild diabetes In only one instance did the fasting blood glucose value exceed 120 mg per 100 ml He found that with increasing levels of fasting blood glucose the frequency of normal tolerance tests decreased and the frequency of abnormal tests increased The relation does not appear to be strong with high frequencies of equivocal or abnormal tests in the range 71 to 90 mg per 100 ml for fasting blood glucose In the present study there was a similar correlation between increasing fasting blood glucose levels and decreasing IVGT the correlation being weak (R = —0 12) This bears a certain clinical implication, as in these subjects the rather high fasting blood glucose levels 90 to 100 mg per 100 ml were of small predictive value as regards the corresponding k values

VI

INTRAVENOUS GLUCOSE TOLERANCE IN MYOCARDIAL INFARCTION, ANGINA PECTORIS, AND INTERMITTENT CLAUDICATION

Introduction

The relation of glucose tolerance to ischaemic cardiovascular disease (ID) has previously been studied mainly in survivors from myocardial infarction In some of these investigations the patient groups have been small poorly defined and limited as to age and sex The numbers of previous myocardial infarctions as well as the interval between the infarction and the glucose tolerance test have varied and the clinical implications of the glucose tolerance have not been evaluated Also glucose tolerance has almost exclusively been tested with oral methods These and other circumstances motivated an investigation of intravenous glucose tolerance (IVGT) in ID

For reasons given in the introductory chapter this investigation was limited to patients with myocardial infarction angina pectoris and intermittent claudication The emphasis is on the results in the patients under A 1 i e the survivors from a first myocardial infarction at the Seraphimer Hospital during the time of the present study as they for certain purposes constituted the most appropriate group The subjects without clinical signs of cardiovascular disease in Chapter V served as a control group The criteria for the classification of the results of the intravenous glucose tolerance test (IVGTT) have been discussed in Chapter IV

Material See Chapter II

Methods See Chapter III

Results

Distribution of k values

The distributions of k values in the 4 patient groups with ID are shown in fig 1 as is the corresponding distribution in the controls In the patients under A 1 the time between admission for an acute myocardial infarction and the IVGTT in fig 1 was 3 to 6 weeks in 166 patients 3 to 20 days in 22 patients and 3 and 5 months respectively in 2 patients In these latter 24 patients no IVGTTs had been performed during the 3 to 6 weeks interval In the patients under A 2 the time between admission for an acute myocardial infarction and the IVGTT always exceeded 3 weeks In the remaining patients the k values were derived from their first IVGTTs The distributions of the k values in the 4 groups of patients with ID did not differ significantly from each other The distributions appear asymmetrical and their normality was uniformly rejected ($P<0.001$ in all instances) The mean k values of groups A 1—4 were 1 10 1 19 1 25 and 1 15 respectively which values all differed significantly from 1 53 of the controls ($P<0.001$ in all instances) Differences also occurred within the range of normal k values on comparison of the patients with ID to the controls Thus in the patients under A 1 only 22 per cent of the normal k values were higher than 1 50 as compared to 50 per cent in the controls ($P<0.001$)

The mean ages and k values and the per cent frequencies of diabetic borderline

Morse et al (1960) obtained lower OGT and IVGT (if k values are calculated from the absolute blood glucose values in their tables) in 11 obese women than in controls Finally, in the Kristianstad survey (1964) there occurred a positive correlation between bodyfat and blood sugar level after ingestion of glucose in men aged 40—59 and 60—79 and in women aged 40—59 In the younger men and older women no such tendency was found, while among younger women the correlation appeared to be negative

The findings in these reviewed studies have been conflicting and sometimes inconclusive as regards the association between obesity and oral glucose tolerance To some extent these discrepancies may have been due to different methods and criteria for the interpretation of the results, and to differences in the selections studied The present investigation of subjects without cardiovascular disease did not shown a relation between obesity and IVGT Comparisons with the above studies are difficult to make, but a further discussion will be given in the next chapter

Hypertension was of no influence on the IVGT of the subjects in the present study *Oral glucose tolerance in hypertension* was investigated by O Hare (1920), Drazin (1953) and Nye (1964), but no control groups were included

In 1963 Frethem studied the relation of fasting blood glucose level to the oral glucose tolerance curve in 401 subjects in most of whom there was a suspicion of mild diabetes In only one instance did the fasting blood glucose value exceed 120 mg per 100 ml He found that with increasing levels *of fasting blood glucose the frequency of* normal tolerance tests decreased and the frequency of abnormal tests increased The relation does not appear to be strong with high frequencies of equivocal or abnormal tests in the range 71 to 90 mg per 100 ml for fasting blood glucose In the present study there was a similar correlation between increasing fasting blood glucose levels and decreasing IVGT, the correlation being weak ($R = -0.12$) This bears a certain clinical implication as in these subjects the rather high fasting blood glucose levels 90 to 100 mg per 100 ml were of small predictive value as regards the corresponding k values

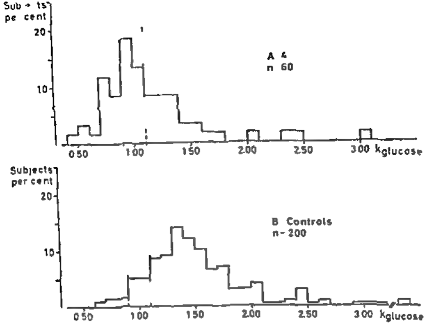

Fig 1

Table 1 IVGT mean k values and ages of patients with ID and controls

	n	IVGT per cent			Mean k value (range)	Mean age years
		Diabetic	Borderline	Normal		
Myocardial infarction A 1	190	.9	31	40	1 10 (0 47—3 00)	61
Myocardial infarction A 2	160	30	23	47	1 19 (0 49—3 47)	57
Angina pectoris A 3	120	34	15	51	1 5 (0 6.—4 80)	58
Intermittent claudication A 4	60	27	31	4[illegible]	1 15 (0 50—3 01)	60
A 1—4	530	31	25	44	1 17 (0 47—4 80)	59
Control group	00	4	10	86	1 53 (0 66—3.85)	5[illegible]

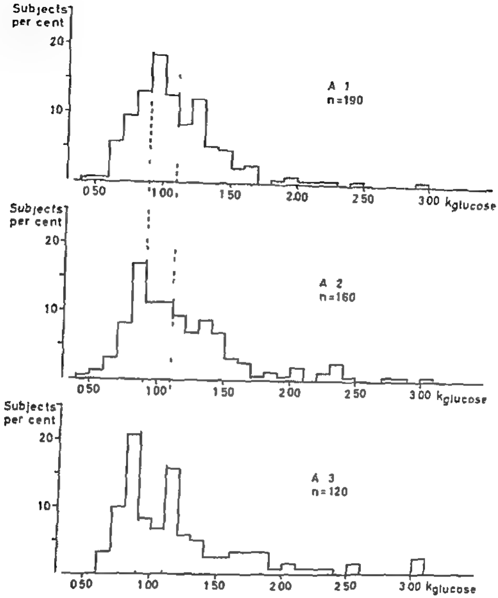

Fig 1 Distributions of k values in patients with ID and controls Groups A 1—4 are described in Chapter II

and normal IVGT of the subjects in fig 1 are further illustrated in table 1

The patients under A 2—4 were selected either by myself or by colleagues Possible differences as regards the principles for selection were of no influence on the results The mean k values of the patients selected by myself in each of the 3 groups were 1 17 1 22 and 1 11 respectively as compared to 1 21 1 35 and 1 25 for those patients selected by my colleagues no difference being significant

The duration of ID in the patients under A 2—4 varied considerably but this did

Table 2 Means, ranges and distributions of k values by age in 193 survivors from a first myocardial infarction

Age	n	IVGT per cent			k value	
		Diabetic	Borderline	Normal		Range
≤ 49	25	17	36	52	1.19	0.69—1.96
50—69	126	29	30	41	1.11	0.47—3.00
≥ 70	39	46	29	26	1.01	0.63—2.41

the 340 patients under A 2—4 is illustrated in table 3. A rank correlation between increasing age and decreasing IVGT was obtained ($R = -0.15$, $P < 0.01$). In this group the distribution of the k values for the patients aged 49 and below differed from that of the patients aged 50 to 69 ($P < 0.01$). Otherwise the results in these patients were similar to those in the patients under A 1.

Sex, diabetic heredity, obesity, hypertension, and IVGT

The relation between *sex and IVGT* in the patients under A 1 is shown in table 4. As regards the frequencies per cent of diabetic, borderline and normal k values or their distributions, no significant differences occurred between the males and the females, their mean k values being 1.09 and 1.14 respectively.

Table 3 IVGT in relation to age in 340 patients with ID (A 2—4)

k value	30—39	40—49	50—59	60—69	70—79	80—89
4.01—5.00		1	1			
3.01—4.00		1	1	1		
2.01—3.00	1	4	10	6		
1.51—2.00	3	9	1	7	1	
1.11—1.50	–	1	50	6	7	
0.91—1.10	3	8	27	23	12	1
≤ 0.90	1	9	38	43	13	

Age, years

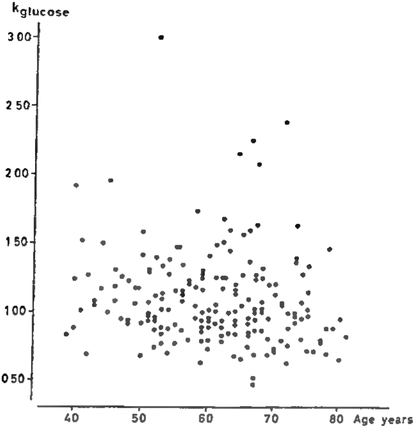

Fig 2 Relation between age and IVGT in 190 survivors of a first myocardial infarction

not affect the distributions of the k values Each of the 3 groups was subdivided, the dividing point being the median duration of ID The mean k values of the patients with the longer duration were 1 16 1 23 and 1 14 respectively in each of the groups as compared to 1 22 1 27 and 1 17 for those with the shorter duration no difference being significant

Age and IVGT

The relation between age and IVGT in the 190 patients under A 1 is shown in fig 2 the k values being the same as those presented in fig 1 A rank correlation existed between increasing age and decreasing IVGT (R = —0 22 P<0 01) In analogy with the esults obtained in the control group, the distribution of the k values in th patients aged 70 years or more differed significantly from those of the patients aged up to 49 years and 50 to 69 years (P<0 01 and 0 02>P>0 01 respectively) whereas the k values of the latter groups did not differ significantly from each other The ranges means and per cent distributions of diabetic borderline and normal k values in these age groups are shown in table 2 The mean k values were 1 19 1 11 and 1 01 respectively and the corresponding k values in the control group were 1 66 1 51 and 1 37 respectively the differences being significant (P<0 001 in all instances)

The relation between age and IVGT in

Table 5. IVGT and diabetic heredity, obesity and hypertension in patients with ID

	A 1				
	n	IVGT per cent			Mean k value
		Diabetic	Borderline	Normal	
1. Diabetic heredity only	19	26	32	42	1.06
2. Obesity only	34	41	32	27	1.07
3. Hypertension only	23	30	22	48	1.19
4. Combinations of 1, 2, 3	9	28	48	24	1.01
5. Absence of 1, 2, 3	85	26	27	47	1.13
	A 2—4				
1. Diabetic heredity only	31	29	23	49	1.13
2. Obesity only	59	44	14	42	1.09
3. Hypertension only	35	25	29	46	1.19
4. Combinations of 1, 2, 3	40	55	17	28	1.02
5. Absence of 1, 2, 3	175	23	23	54	1.31

$P < 0.001$, respectively). Otherwise no significant differences occurred.

Signs of *cardiovascular disease preceding the acute myocardial infarction* for at least one month had occurred in 94 of the patients under A 1, their mean age being 61 years. In 72 of these patients they consisted of angina pectoris, in 4 patients of intermittent claudication, in 3 patients of both angina pectoris and intermittent claudication, in 10 patients of abnormal effort dyspnea considered to be of cardiac origin, in 4 patients of cerebro-vascular episodes and in 1 patient of severe attacks of ventricular tachycardia. Their mean k value was 1.09, which was of no significant difference from 1.11 of the patients without signs of cardiovascular disease preceding the myocardial infarction.

45 patients under A 1 had *neither diabetic heredity, obesity, hypertension nor signs of cardiovascular disease preceding the*

Table 4 Sex diabetic heredity obesity hypertension and IVGT in 190 survivors from a first myocardial infarction

	Number of Patients	IVGT per cent Diabetic	Borderline	Normal	Mean K	Mean age
Males	150	30	30	40	1 09	60
Females	40	28	32	40	1 14	66
Diabetic heredity	31	26	39	35	1 08	61
Obesity	60	37	36	27	1 03	63
Hypertension	47	26	40	34	1 08	61
Total	190	29	31	40	1 10	61

In the patients under A 2—4, on the other hand, the mean k values of the 288 males and the 52 females were 1 18 and 1 40 respectively, the difference being significant ($P < 0\ 01$) Their mean ages were 58 and 60 years respectively, this difference not being significant

The relation between *IVGT and diabetic heredity, obesity and hypertension* in the patients under A 1 is also shown in table 4 No significant differences in the IVGT were obtained for the patients with diabetic heredity as compared to those without nor for the patients with hypertension as compared to those without

Of the patients under A 2—4 the 43 patients with diabetic heredity had a mean k value of 1 10 as compared to 1 24 of those without and the 69 patients with hypertension had a mean k value of 1 13 as compared to 1 23 of those without no difference being significant

The k values of the obese patients under A 1 differed from those of the non obese ($0\ 02 > P > 0\ 01$) the mean values being 1 03 and 1 13 respectively The corresponding difference was more pronounced in groups A 2—4 in which the 95 obese patients had a mean k value of 1 04 as compared to 1 28 for the non obese ($P < 0\ 001$) These differences were not the result of age as the mean age of the obese patients under A was 60 years as compared to 59 years of the non obese the difference not being significant

In a further attempt to evaluate the association between IVGT and diabetic heredity obesity and hypertension the patients under A 1 and A 2—4 with only one of these features combinations of them or the absence of them were compared with each other The results are shown in table 5 The mean k values of the patients with obesity only or with more than one of the above features each differed significantly from that of the patients without any of these features both under A 1 ($P < 0\ 05$ in both instances) and A 2—4 ($P < 0\ 01$ and

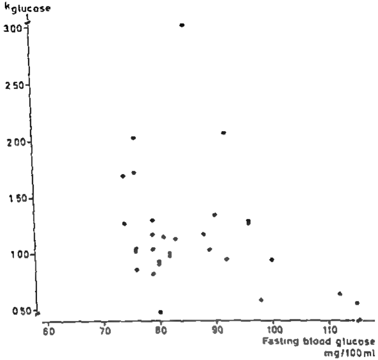

Fig 4 Relation between fasting blood glucose and k value in 78 of the patients in fig 3 ▪ retest more than one year later

last IVGTTs were chosen when more than one had been performed in a patient The results are illustrated in fig 3 A negative rank correlation between the fasting blood glucose level and the k value was still obtained ($R = -0\,36$ $P < 0\,01$) In the control group the corresponding correlation was weaker ($R = -0\,12$ $P < 0\,05$) as shown in the foregoing chapter

The mean fasting blood glucose level of the patients under A 1 represented in fig 3 was 87 mg per 100 ml range 63 to 123 which was of no significant difference from 83 mg per 100 ml range 60 to 118 of the control group At corresponding fasting blood glucose levels the IVGT was lower in the patients under A 1 than in the controls ($P < 0\,05$ at the lowest glucose level $P < 0\,001$ at the higher glucose levels) as illustrated in table 6 In the subjects with fasting blood glucose levels 90 mg per 100 ml and higher only 16 per cent of those under A 1 had normal k values as compared to 77 per cent of those in the control group

The corresponding relations between fasting blood glucose levels and k values for the patients under A 2—4 are shown in table 7 in which the figures represent the results from the first IVGTT in each patient using the glucose oxidase method A negative rank correlation was obtained ($R = -0\,25$ $P < 0\,001$) The mean fasting blood glucose level was 82 mg per 100 ml range 62 to 130

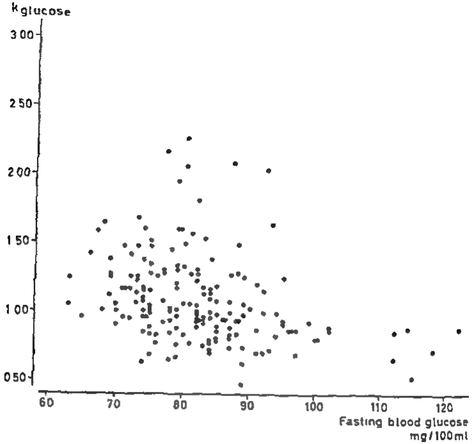

Fig 3 Relation between fasting blood glucose and k value in 176 survivors from a first myocardial infarction

acute myocardial infarction, their mean age being 60 years Their mean k value was 1 16 which did not differ significantly from 1 08 of the patients with one or more of these features

Fasting blood glucose and IVGT

In 176 of the patients under A 1 represented in fig 1 blood glucose was determined by the glucose oxidase method The relation between the fasting blood glucose level and the k value in these patients is shown in fig 3 Those patients who had been tested only by the Hagedorn method for blood sugar determination or less than 3 weeks after admission were excluded In 154 of the patients represented in fig 3 the tests were performed during the 3 to 6 weeks interval after the myocardial infarction The remaining 22 patients had not been tested using the glucose oxidase method during this interval They are represented by the results from their first IVGTTs performed later There existed a negative rank correlation between fasting blood glucose level and k value (R = —0 41 $P < 0.001$) To ascertain whether this correlation changed with time it was also calculated for the 78 patients who had been retested more than 1 year after the myocardial infarction The results from the

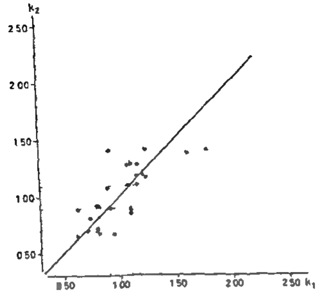

Fig 5 Relation of k values obtained 3 to 20 days after the acute myocardial infarction (k_1) to k values obtained later (k)

were differences obtained for the above 37 and 14 patients separately 11 patients were tested 3 to 7 days after hospitalisation and again 3 to 6 weeks later The mean k values on both occasions were 1 14 Blood glucose had been determined by the glucose oxidase method at both tests in 10 of the patients The mean fasting levels were 86 and 85 mg per 100 ml respectively the difference not being significant

Glucose analysis was routinely undertaken on urine samples from the patients under A 1 during the first 3 days of hospitalisation Unfortunately the sampling was not made uniformly and in most cases only on morning urine specimens In 29 patients *glucosuria* was found once or twice but not in the following samples The mean k value of these patients was 1 00 as a compared to 1 12 of the patients without detected glucosuria, the difference not being significant

Diuretics and IVGT

During these last years diuretics such as thiazides and chlorthalidone have been found to lower glucose tolerance Treatment with these drugs occurs rather frequently in patients with ID and its effect on the present results was investigated 26 patients under A 1 and 8 patients under A 2—4 were tested with and without such treatment which they in all cases received for therapeutical reasons The results are shown in fig 6 The mean k values of the patients when they were and were not receiving these drugs were 1 17 and 1 08 respectively the difference not being significant Another 17 patients under A 1 were receiving diuretics throughout the time of the present study The mean k value of their first tests was 1 00 which did not differ significantly from 1 11 of the patients not receiving diuretics

Table 6 Mean k values and ranges in survivors from a first myocardial infarction and controls classified by fasting blood glucose

Fasting blood glucose mg/100 ml	Myocardial infarction (A 1)			Controls		
	n	K values		n	K values	
		Mean	Range		Mean	Range
≥ 90	31	0.93	0.52—2.05	44	1.44	0.66—3.17
70—89	134	1.24	0.47—3.00	146	1.55	0.77—3.85
≤ 69	11	1.27	0.96—1.65	10	1.62	1.14—2.57

Table 7 IVGT in relation to fasting blood glucose in 334 patients with ID (A 2—4)

k value	60—69	70—79	80—89	90—99	100—109	110—119	120—129	130—139
4.01—5.00	1	1						
3.01—4.00		3						
2.01—3.00		7	10	2				
1.51—2.00	6	11	13	3				
1.11—1.50	13	34	41	10	2			
0.91—1.10		13	35	23				
≤ 0.90	2	22	34	29	7	7	4	1

Fasting blood glucose mg per 100 ml

Acute myocardial infarction glucosuria and IVGT

In 51 patients under A 1 an IVGTT was performed within 3 weeks of hospitalisation. In 37 of them this test was compared to one performed 3 to 6 weeks after hospitalisation the minimum interval between the two tests being 2 weeks. In 14 patients the second test was performed from 3 months up to 3 years later. The results are illustrated in fig 5. 27 patients had higher k values on the second test and 24 had lower values. The mean k values of the first and the second tests were 1.04 and 1.09 respectively the difference not being significant. Of the 19 patients with initially diabetic IVGT 4 had borderline and 2 normal second tests. Of the 15 patients with borderline IVGT 7 had become diabetic and 4 normal and of the 17 initially normal ones 3 had become borderline and no one diabetic. Nor

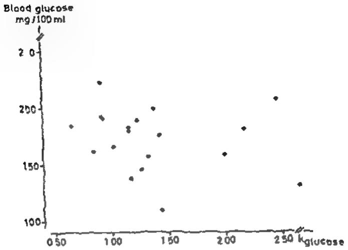

Fig 7 Relation between the maximum blood glucose value at 3) 60 or 90 minutes of the oral glucose tolerance test (OGTT) and the k value of the IVGTT

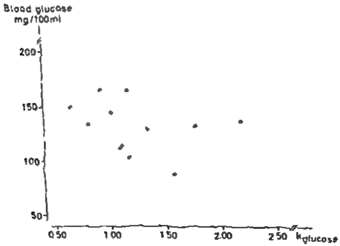

Fig. 6 Relati n between the 1 0 minute bl od glucose value of the OGTT and the k value of the IVGTT

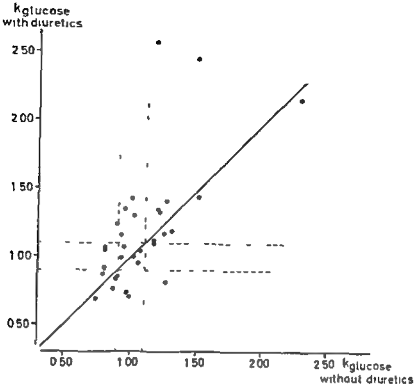

Fig 6 Relation of k values in patients with ID with and without *medication with diuretics*

Oral glucose tolerance and IVGT

The relation of the oral glucose tolerance (OGT) to the IVGT was investigated in patients with ID, as previous authors on glucose tolerance in such patients mainly have employed the former method 43 patients under A were tested with both *methods under comparable conditions* There were 33 men and 10 women, mean age 61 range 34 to 80 years selected with regard to their k values The mean k value was 1 27 range 0 52 to 3 00 12 patients had diabetic 11 borderline and 20 normal IVGT The interval between the oral glucose *tolerance test (OGTT)* and the IVGTT ranged from 1 week to 6 months The result of the test giving the shortest interval was selected when more than one IVGTT had been performed in a patient The OGTT is described in Chapter III

In each patient the k value was related to the following blood glucose values of the OGT

1 The maximum value at 30 60, or 90 minutes
2 The 120 minute value
3 The 150 *minute* value
4 The mean of 1 2 and 3
5 The per cent change between 1 and 2
6 The per cent change between 1 and 3

The results of 1 to 4 are shown in figs 7 8 9 and 10 In these instances negative *rank correlations were obtained* (R = —0 47 P<0 01 R = —0 61 P<0 001 R = —0 54 P < 0 001 and R = —0 62 P < 0 001 respectively) Under 6 a correlation was also obtained (R = —0 31 P<0 05) but not under 5

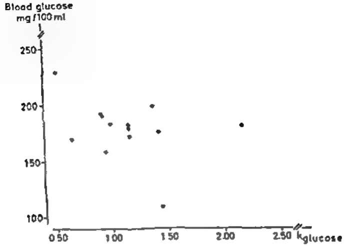

Fig 7 Relation between the maximum blood glucose value at 30 60 or 90 minutes of the oral glucose tolerance test (OGTT) and the k value of the IVGTT

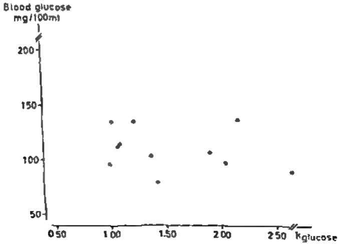

Fig 8 Relation between the 1 0 minute blood glucose value of the OGTT and the k value of the IVGTT

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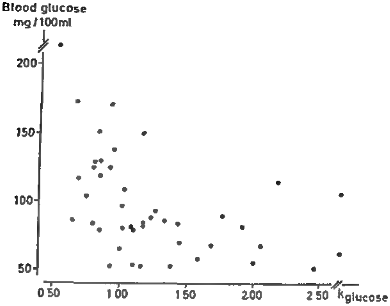


Fig 9 Relation between the 150 minute blood glucose value of the OGTT and the k value of the IVGTT

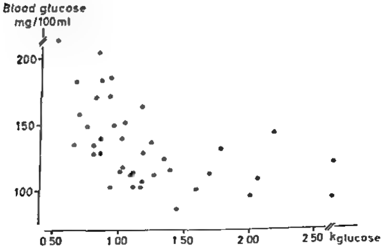
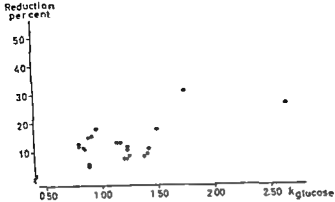


Fig 10 Relation between the mean of the 3 blood glucose values of fig 7 8 9 and the k value of the IVGTT



ig 11 Relation between the reduction per cent of fasting blood glucose at 10 minutes of the intra enous insulin sensitivity test (IST) and the k value of the IVGTT

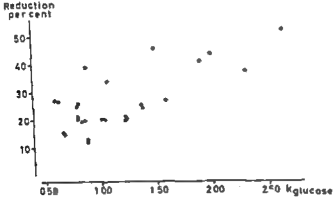


Fig 1 Relation between the reduction per cent of fasting blood glucose at 20 minutes of the IST and the k value of the IVGTT

Intravenous insulin sensitivity and IVGT

The relation of the intravenous insulin sensitivity (IS) to the IVGT was studied in patients with ID to find out if the frequently encountered low IVGT in such patients was associated with insensitivity to the hypoglycemic action of intravenously administered insulin 57 patients under A were selected on account of their k values There were 51 men and 6 women mean age 59 range 40 to 76 years The mean k value was 1 11 range 0 60 to 2 64 22 patients had diabetic, 12 borderline and 23 normal IVGT The interval between the intravenous insulin sensitivity test (IST) and the IVGTT ranged from 1 week to 6 months The result from the test giving the shortest interval was selected when more than one IVGTT had been performed in a patient The IST is described in Chapter III

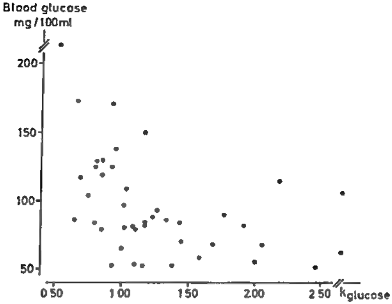


Fig 9 Relation between the 150 minute blood glucose value of the OGTT and the k value of the IVGTT

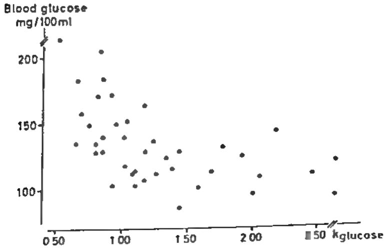


Fig 10 Relation between the mean of the 3 blood glucose values of fig 7 8 9 and the k value of the IVGTT

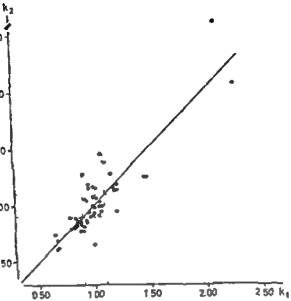


Fig 14 Relation between k values 3 to 6 weeks after acute myocardial infarction (k_1) and k values *from retests within 6 months* (k)

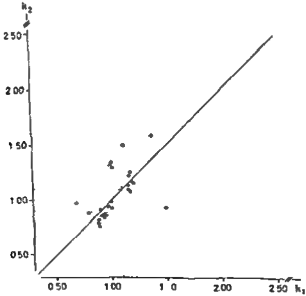


Fig 15 Relation between k values 3 to 6 weeks after acute myocardial infarction (k_1) and k values from retests 7 [illegible] months later (k)

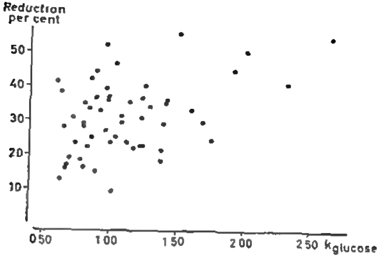


Fig 13 Relation between the reduction per cent of fasting blood glucose at 30 minutes of the IST and the k value of the IVGTT

The relation of the IS to the IVGT is illustrated in figs 11, 12 and 13, in which the per cent reductions of the fasting blood glucose levels at 10 20, and 30 minutes have been plotted against the k values At these observation times rank correlations between these variables were obtained ($R = 0.47$, $P < 0.001$, $R = 0.52$, $P < 0.001$, and $R = 0.32$, $0.02 > P > 0.01$) No correlations were obtained at 40 50, and 60 minutes

Variation of IVGT

The variation of the IVGT with time has primarily been studied in the patients under A 1 74 *patients were tested 3 to 6* weeks after admission for the acute myocardial infarction and were retested *within 6 months* The relation between the k values is shown in fig 14 Of 21 patients with initially diabetic k values 2 had normal values at retest and of 23 patients with a *normal* k value 1 had a diabetic value at *retest* Of 30 patients with borderline k values 10 had normal and 5 diabetic values at retest In 71 per cent of the patients the results of both tests were in accordance The mean k values of the *first* and *second tests* were 1 08 and 1 13 respectively the difference not being significant 80 per cent of the differences between the k values of the first and second tests ranged from —0 26 to 0 26 24 patients had been retested within 4 weeks and the mean k value at both instances was 1 17 the range for 80 per cent of the differences being —0 25 to 0 20

65 patients were correspondingly retested *7 to 24 months later* The results are shown in fig 15 When more than one test had been performed in the same patient during this time the k value from the last test was *chosen for comparison* Of the 12 patients with initially diabetic k values none had a normal value at retest and of the 31 patients with normal values 3 had diabetic values at retest Of 22 patients with borderline k values 7 had normal and 7 diabetic values at retest In 60 per cent of the patients the results of both tests were in accordance The mean k values of the first and second tests were 1 16 and 1 19 respectively the difference not being significant 80 per cent

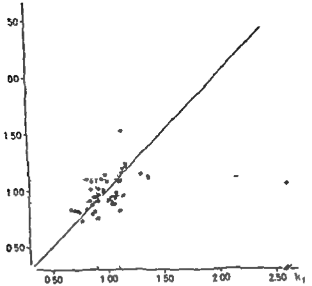


Fig 1* Relation between the first k values in patients under A 2—4 (k_1) and k values from retests more than 24 months later (k)

patients had borderline k values in the latest retest 5 of whom only on this occasion 2 patients had normal k values 1 of whom only on this occasion The IVGT of the 43 *patients with initially borderline k values* remained the same in 19 (44 per cent) and of these 1 had had normal and 1 diabetic k values in between. 13 patients had a diabetic k value at the latest retest 6 of whom only on this occasion 11 patients had normal k values 7 of whom only on this occasion The IVGT of the 50 *patients with*

Table 8 IVGT at last retest in patients with ID (A 1)

Initial IVGT	Number of patients				
	Total	Retested	IVGT at last retest		
			Diabetic	Borderline	Normal
Normal	75	50	5	9	36
Borderline	59	43	13	19	11
Diabeti	56	36	28	6	2
T tal	190	1 9	46	34	49

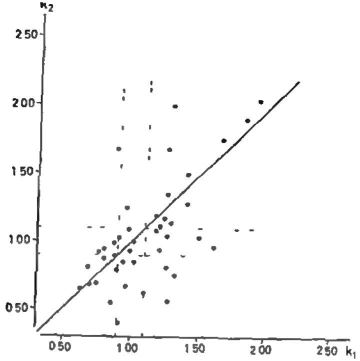


Fig 16 Relation between k values 3 to 6 weeks after *acute myocardial infarction* (k_1) and k values from retests more than 24 months later (k)

of the differences between the k values ranged from —0·23 to 0·38

42 patients were retested *more than 24 months later* The results are shown in fig 16 When more than one test had been performed in the same patient during this time the last k value was chosen for comparison Of the 12 patients with initially diabetic k values 1 had a normal value at retest, and of the 20 with normal k values 3 had diabetic values at retest Of 10 patients with borderline k values 1 had a normal and 5 diabetic values at retest In 56 per cent of the patients the results of both tests were in accordance The mean k values of the first and second tests were 1·11 and 1·06 respectively the differences not being significant 80 per cent of the differences between the k values ranged from —0·47 to 0·43

69 patients under *A 2—4* were retested *more than 24 months* after their initial IVGTT and the result is shown in fig 17 These results do not differ essentially from those obtained in the patients under A 1, but the variation of the k values appears to be smaller In 70 per cent of the patients the results of the two tests were in accordance The mean k values of the first and second tests were 1·08 and 1·03 respectively the difference not being significant 80 per cent of the differences between the k values ranged from —0·19 to 0·22

Of the 190 patients under *A 1* all in all 129 were retested after their hospitalisation A comparison of the initial and last k values in these patients is given in table 8 A total of 227 retests were performed The IVGT of the *36 patients with initially diabetic k values* remained the same in 28 (77 per cent) and of these 2 had had a borderline and 1 a normal k value in between 6

Table 9 Long term survival after a first myocardial infarction in relation to IVGT

IVGT	Patients			Observation months		
	Dead	Alive	Total	Dead	Alive	Total
Normal	9	66	75	42	[illegible]	2516
Diabetic and Borderline	31	84	115	774	2701	3475
Total	40	150	190	1016	[illegible]	5991

Long term survival and IVGT

The *prognostic implication* of the IVGT as regards long term survival was evaluated for the 190 patients under A 1. Information about all of them was last obtained in January 1966 when the *minimum* observation time from the acute episode was 3 months. The patients were classified according to their k values represented in fig. 1. Of the 56 patients with diabetic IVGT 21 (38 per cent) were dead, of the 59 with borderline IVGT 10 (17 per cent) and of the 75 with normal IVGT 9 (12 per cent). Of these last 9 patients 7 were men and 2 women with k values ranging from 1.13 to 1.65, these not differing from the k values of the surviving patients with normal IVGT. For the calculation of the survival rate the patients with diabetic and borderline IVGT were considered to comprise one group with low IVGT as the number of patients was too small to allow statistical analysis of these results with the patients divided into 3 groups. The fusion of these groups seemed natural as there occurs clinical diabetes within the range of borderline k values and as the mean k value of the 190 patients under A 1 was 1.10, i.e. the upper limit of the borderline k values. Thus, of the 115 patients with low IVGT 31 (27 per cent) were dead, of whom 26 were men and 5 women. The total numbers and observation months of the patients as alive or dead in these two groups are shown in table 9. The patients with low IVGT differed in both these respects from those with normal IVGT ($0.02>P>0.01$ and $P<0.001$ respectively). The mean age of the patients with low IVGT was 62 years as compared to 59 years of those with normal IVGT. To minimize the effect of age differences on survival the patients were divided by ages up to 69 years and 70 years or more. After this division the mean ages differed by 1 year for the patients with low and normal IVGT in both age groups. Of the 151 *younger patients there* were 64 with normal IVGT *of whom* 7 had died and 87 with low IVGT of whom 19 had died, the difference not being significant. On the other hand the groups differed as regards survival time ($P < 0.001$). Corresponding results were obtained *for the* 39 older patients. The *survival rates for the* two groups in per cent of *patients* and observation months are shown in fig. 18.

It is seen that the survival rates of the patients with low IVGT are lower *than those of the* patients with normal IVGT in both *age groups. In the* younger patients the

initially normal k values remained the same in 36 (72 per cent) and of these 3 had a borderline k value in between 9 patients had *borderline k values* at the latest retest 6 of whom only on this occasion 5 had diabetic k values *2 of whom only on this* occasion

Development of clinical diabetes

When possible urine specimens have been tested for glucose once yearly in the patients with ID

Three of the patients under A 1 are known to have developed *clinical diabetes* according to the definition in Chapter IV All were obese women 51, 69 and 72 years old at the time of their myocardial infarction The youngest of them had a borderline k value and fasting blood glucose 79 mg per 100 ml at the first test Two and a half *years later she had glucosuria fasting blood* glucose 112 mg per 100 ml and k = 0 67 The other two had diabetic k values and fasting blood glucose around 110 mg per 100 ml at the first test In one of them diabetes was diagnosed after 2 months and in the other after 2 years

Another patient under A 1 a non obese man, 59 years old at the time of the myocardial infarction *has probably developed* clinical diabetes At the first test his fasting *blood glucose* was 121 mg per 100 ml and k = 0 63 but several urine specimens were glucose free 2 years afterwards he visited a physician for a routine health control Glucosuria was diagnosed in one sample after which he was prescribed 2 tablets of tolbutamide daily, but was controlled no further One and a *half years later he* was retested had fasting blood glucose 78 mg per *100 ml and* k = 0 65 He had then not *taken* tolbutamide for the last 24 hours Withdrawal of tolbutamide for 2 weeks did not produce glucosuria After this the patient continued the treatment He has not been examined since

Two of the patients under A 2—4 are known *to have* developed diabetes but this group has been followed less regularly than A 1 *One of them* was an *obese* man 61 years of age, with fasting blood glucose 100 mg per 100 ml and k = 0 78 at the time of the first test At retest more than 2 years later he had fasting blood glucose 119 mg per 100 ml and k = 0 73 At that time several urine samples were glucose free but glucosuria developed 3 months later The other was an obese woman 67 years old with fasting blood glucose 150 mg per 100 ml and k = 0 64 in whom diabetes was *diagnosed 5 years later*

Ophthalmoscopies were undertaken in 123 out of 134 *patients* under *A* 1 living in Stockholm from September 1965 to January 1966 After dilatation of their pupils with an ophthalmoplegic (Cyclogyl) the fundi were examined by myself for at least 5 minutes each eye using both the white and the green light of the ophthalmoscope For this investigation only abnormalities suggestive of diabetic retinopathy in the form of dark *red spots (microaneurysms)* haemorrhages and exsudates were noted All patients in whom discolorations of any size or shape were seen in the retina were further examined by an ophthalmologist

In the male patient described above with probable clinical diabetes multiple bilateral dark red spots and *bilateral white yellowish* exsudates suggestive of diabetic retinopathy *were seen* Otherwise findings suggestive of diabetic retinopathy were not found in these patients under A 1 nor in another 100 patients examined under A 2—4

Table 9 Long term survival after a first myocardial infarction in relation to IVGT

IVGT	Patients			Observation months		
	Dead	Alive	Total	Dead	Alive	Total
Normal	9	66	75	242	2274	2516
Diabetic and Borderline	31	84	115	774	2701	3475
Total	40	150	190	1016	4975	5991

Long term survival and IVGT

The *prognostic implication* of the IVGT as regards long term survival was evaluated for the 190 patients under A 1 Information about all of them was last obtained in January 1966 when the minimum observation time from the acute episode was 3 months The patients were classified according to their k values represented in fig 1 Of the 56 patients with diabetic IVGT 21 (38 per cent) were dead of the 59 with borderline IVGT 10 (17 per cent) and of the 75 with normal IVGT 9 (12 per cent) Of these last 9 patients 7 were men and 2 women with k values ranging from 1 13 to 1 65 these not differing from the k values of the surviving patients with normal IVGT For the calculation of the survival rates the patients with diabetic and borderline IVGT were considered to comprise one group with low IVGT as the number of patients was too small to allow statistical analysis of these results with the patients divided into 3 groups The fusion of these groups seemed natural as there occurs clinical diabetes within the range of borderline k values and as the mean k value of the 190 patients under A 1 was 1 10 i e the upper limit of the borderline k values Thus, of the 115 patients with low IVGT 31 (27 per cent) were dead of whom 26 were men and 5 women The total numbers and observation months of the patients as alive or dead in these two groups are shown in table 9 The patients with low IVGT differed in both these respects from those with normal IVGT (0 02>P>0 01 and P<0 001 respectively) The mean age of the patients with low IVGT was 62 years as compared to 59 years of those with normal IVGT To minimize the effect of age differences on survival the patients were divided by ages up to 69 years and 70 years or more After this division the mean ages differed by 1 year for the patients with low and normal IVGT in both age groups Of the 151 younger patients there were 64 with normal IVGT of whom 7 had died and 87 with low IVGT of whom 19 had died the difference not being significant On the other hand the groups differed as regards survival time (P < 0 001) Corresponding results were obtained for the 39 older patients The survival rates for the two groups in per cent of patients and observation months are shown in fig 18

It is seen that the survival rates of the patients with low IVGT are lower than these of the patients with normal IVGT in both age groups In the younger patients the

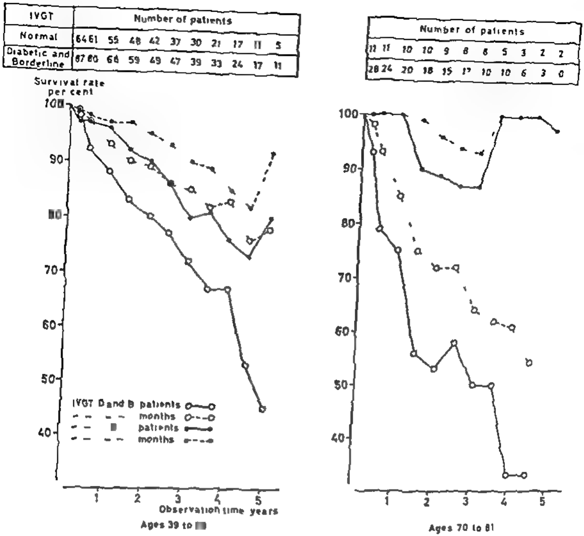


Fig 18 Long term survival rates in two age groups of 190 survivors of a first myocardial infarction classified by IVGT

survival rates in months differed between those with low and normal IVGT at 12 18, 24 30 36 and 42 months ($P < 0.001$ in all instances), not at 48 months but at 54 and 60 months ($P < 0.005$ and $P < 0.001$ respectively) In the older patients corresponding differences were obtained from 12 to 42 months ($P < 0.001$ in all instances) Finally, the corresponding cumulated survival rates (Cutler & Ederer 1958) of the 190 patients under A 1 are shown in fig 19

Discussion

Statistical analysis in medical research is at present generally carried out with methods intended for normal distributions of values and such distributions are required for the validity of the results thus obtained The distributions of k values in the patients with ID and in the control group were similarly asymmetrical The k value was the principal variable of the present study, wherefore non parametric methods were chosen for statistical analysis as they apply to any distribu

IVGT	Number of patients										
Normal	75	72	65	[illegible]	51	45	[illegible]	26	20	12	7
Diagnostic and Borderline	115	104	88	77	64	59	49	43	30	[illegible]	11

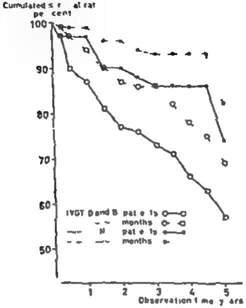


Fig 19 Cumulated survival rates in 190 survivors of a first myocardial infarction classified by IVGT

tion of values including the normal It is possible to transform a certain skewness of a distribution of values into normality by using logarithms This was not tried in the present study as the use of nonparametric methods could not entirely be avoided thereby and I wished to perform statistical analysis as uniformly as possible The analytical power of significance of non parametric methods is somewhat lower than that of parametric methods but this is of no disadvantage in a study such as the present one

The *distributions of k values* in the patients under A 1 2 3 and 4 did not significantly differ from each other which was considered remarkable Of these patients the 190 under A 1 were survivors from a first myocardial infarction at the Seraphimer hospital during the time of the present study The other three groups consisted of patients with different manifestations of ID who had not been uniformly selected Their common feature was ID which was the foremost reason for my selection of them The remaining patients were selected by colleagues for various reasons not always known to me Their treatment had not been uniform some required hospitalisation at the time of the test and the durations and clinical courses of their diseases varied considerably However these factors did not

influence the results This is further emphasized by the fact that the variation of the results during the course of the present study has always been insignificant

The IVGT of either the entire patient group under A or of each of the subgroups separately, differed significantly from that of the control group under B This indicates a relationship between low glucose tolerance and ID also in the absence of clinical diabetes The relationship was not only the result of an accumulation of diabetic and borderline k values in these patients but also of low k values within the normal range, as is shown by comparison of the results in the patients under A 1 and the controls

The validity of these observations can of course, be questioned (Ryan et al 1964) and claimed to be the result of selection as neither the patients with ID nor the controls represent true random samples The Seraphimer Hospital receives patients from a non defined population mainly in Stockholm with environments It was shown by Wahlberg (1963) that in the 1950s the patients from this hospital with myocardial infarction did not differ to any great extent from those of other hospitals serving well defined populations as regards sex age, diabetes hypertension and acute mortality There is no reason to believe that these conditions have changed significantly since then, and the patients under A 1 may be considered as representative of survivors from one myocardial infarction in Sweden

None of the groups under A 2—4 differed significantly as regards their IVGT either from each other or from A 1 nor did selection manifestations of ID or the duration of the disease influence the results Therefore it appears probable that a random sample of the population in Stockholm with corresponding manifestations of ID under the same conditions as in the present study, would yield similar results as regards IVGT

The selection and structure of the control group is crucial with regard to the acceptability of a relationship between ID and low glucose tolerance as claimed by the results of the present study A random sample of subjects from Stockholm according to given criteria matched to the patients under A would perhaps have constituted the most appropriate basis for comparisons On the other hand such a sample was not considered to be a pre equisite and was furthermore impossible for me to obtain

The primary criteria for the selection of the control group were the absence of clinical signs of cardiovascular disease and a normal ECG at rest In other studies on carbohydrate metabolism in ID, control groups of healthy and comparatively young subjects were used (Boehle & Schrade 1960 Waddell & Field 1960 Aleksandrow et al, 1962) but this was not thought to be adequate as factors such as age or the presence of disease per se could influence the glucose tolerance Therefore most of the controls were selected while attending some department of the Seraphimer Hospital To be able to evaluate the influence of age in IVGT it was tried to distribute the subjects evenly by age within the ranges commonly met with in ID For natural reasons it was difficult to find a satisfactory number of subjects more than 70 years old under the given premise As there generally exists some limitation of the physical capacity in patients with ID subjects with exceptionally good physical condition were rarely included To ascertain the role of sex as regards IVGT

Table 10 Oral glucose tolerance in ischaemic cardiovascular disease

Author	n	Oral glucose tolerance per cent	
		Abnormal	Normal
Edelmann (1934)	8	75	25
Raab & Rabinowitz (1936)	21	71	29
Goldberger et al (1945)	14	71	29
Bartels & Rullo (1958)	100	59	41
Boehle & Schrade (1960)	154	61	39
Waddell & Field (1960)	47	85	15
Sowton (1962)	30	73	27
Reaven et al (1963)	41	41	59
Tibblin & Cramer (1963)	27	56	44
Fabrykant & Gelfand (1964)	42	64	36
Nye (1964)	63	35	65
Cohen & Shafrir (1965)	43	77	23
Total	590	61	39

almost equal numbers of men and women were preferred to the male preponderance usually encountered in ID Other guiding principles for the sampling were diabetic heredity obesity and hypertension as these features occur frequently in ID Some consequences of the rather arbitrary selection could not be avoided but age was the only factor found to influence the IVGT in the control group It is therefore probable that changes in its composition brought about by other sampling methods would not have affected the results significantly

As up to now the only other investigation on IVGT measured as in the present one in ID was undertaken by Ryan et al (1964) and their results differ from mine They tested 176 working men ages 40 to 60 years 43 of whom had coronary heart disease 73 with a diabetic relative and 60 without a known diabetic relative No significant differences were found between the three groups with regard to the IVGT the total number of K values ranging 0 4 to 2 6 Only a summary has been presented wherefore it has not been possible to compare our results thoroughly The authors concluded that studies made on non homogenous populations must be interpreted with caution On the other hand *Frehner & Wegmann* (1963) using another IVGTT found latent diabetes in 40 per cent of their 27 survivors of myocardial infarction which is in accordance with my result

The results of oral glucose tolerance tests in patients with ID as given by the literature are summarised in table 10 The groups studied by most authors consisted only of survivors from myocardial infarction (Edelmann 1934 Raab & Rabinowitz 1936 Goldberger et al 1945 Sowton 1962 Reaven et al 1963 Tibblin & Cramer 1963, Cohen & Shafrir 1965) whereas those of others also included *patients* with angina pectoris (Boehle & Schrade 1960 Waddell & Field 1960 Nye 1964) and *intermittent* claudication (Boehle & Schrade 1960 Waddell & Field 1960) The patients of Barthels &

influence the results This is further emphasized by the fact that the variation of the results during the course of the present study has always been insignificant

The IVGT of either the entire patient group under A, or of each of the subgroups separately, differed significantly from that of the control group under B This indicates a relationship between low glucose tolerance and ID also in the absence of clinical diabetes The relationship was not only the result of an accumulation of diabetic and borderline k values in these patients but also of low k values within the normal range as is shown by comparison of the results in the patients under A 1 and the controls

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Table 11 Glucose tolerance determined with oral (OGT) and intravenous (IVGT) methods in 43 patients with ID

OGT	IVGT			Total
	Diabetic	Borderline	Normal	
Diabetic	6	4	1	11
Borderline	5	1	6	12
Normal	1	6	13	20
Total	1[illegible]	11	0	43

of carbohydrate metabolism as e g after oral glucose administration factors such as the emptying rate of the stomach (Nisell 1957) intestinal absorption and possibly gastrointestinal hormones (Mc Intyre et al 1965 Pfeiffer et al 1965) influence the results In spite of this only 2 out of the 43 patients showed fully discordant results and most of the overlapping occurred in the borderline groups as could be expected 30 per cent of the patients were normal according to both tests as compared to 47 per cent for each test separately

Few comparisons between the IVGT and OGT in the same subjects have been presented Lundbaek (1960) obtained correlations between the k value and both the 180 minute blood glucose value and the per cent fall of blood glucose from the maximum value to 180 minutes in 45 diabetics Nadon et al (1964) compared OGT with IVGT determined according to Amatuzio et al (1953) wherefore detailed comparisons with the present study are difficult to make but their results seem to be in accordance It appears that their correlation between the k value and the 120 minute blood glucose value corresponds well to that of the present study

The constant finding of low glucose tolerance in patients with ID as reported by others as well as by myself lessens the probability of this being due to selection The results obtained in the populations of Tecumseh (Ostrander et al 1965) and Bedford (Keen et al 1965) as regards the association betwen carbohydrate metabolism and the prevalence of cardiovascular disease lend further support to the validity of the above results

In the epidemiological study from Tecumseh Ostrander et al (1965) found that the proportion of elevated blood glucose levels defined as belonging to the upper quintile of the blood glucose levels obtained 1 hour after the ingestion of 100 g of glucose was significantly highe for the participants with cardiovascular disease than for those without The results of Epstein et al (1965) from the same study suggested that hyperglycemia was an independent risk factor among persons with coronary heart disease in Tecumseh and seemed to be at least as important as either

Rullo (1958) were described as having intermittent claudication only and those of Fabrykant & Gelfand (1964) as having angina pectoris The results of Aleksandrow et al (1962) could not be included in table 10 as the frequencies of abnormal and normal tests were not given Their patients were described as having clinical and electrocardiographic evidence of coronary disease and they had significantly lower OGT than the controls Both male and female patients were tested by Waddell & Field (1960), Sowton (1962), Tibblin & Cramer (1963), Fabrykant & Gelfand (1964) and Nye (1964), only male patients by Cohen & Shafrir (1965) whereas the other authors omit information concerning sex The upper age limit was set at 49 years by Cohen & Shafrir (1965) and 69 by Tibblin & Cramer (1963) In the other reports no such limitations were deliberately set the ages of the patients ranging from 17 (Reaven et al 1963) to 81 years The control groups consisted of 52 healthy men 45 to 64 years of age (Boehle & Schrade 1960) 19 healthy male and female volunteers 21 to 39 years old (Waddell & Field 1960), 35 healthy subjects 20 to 52 years old (Aleksandrow et al 1962), 40 male and female patients of whom some had neoplastic malignant disease 32 to 94 years old (Reaven et al 1963) 28 male and female patients with hypertension but without signs of ID mean age 57 years (Nye 1964) and 36 normal control cases less than 50 years old (Cohen & Shafrir 1965) In the patients with myocardial infarction the time intervals between the acute episode and the OGTT ranged from days to years Of the results in table 10 those of Edelmann (1934), Raab & Rabinowitz (1936), and Sowton (1962) were obtained exclusively during the early phase of hospitalisation and as a rule the latter performed the tests on the morning after admission

The above studies showed similar and high frequencies of abnormal (or diabetic, Edelmann 1934 Goldberger et al 1945, Waddell & Field 1960, Sowton 1962) OGTTs in the patients with ID while the controls had lower frequencies In the total number of 590 patients with ID, 61 per cent of the tests were abnormal and 39 per cent normal These figures are very close to the corresponding 56 and 44 per cent of the present study This is remarkable not only as regards the varying compositions of the groups studied but also as varying oral methods were used

According to the present investigation an association exists between oral and intravenous glucose tolerance Significant correlations were obtained between on the one hand the k value and on the other hand either the highest blood glucose value at 30 60 or 90 minutes the 120 minutes value the 150 minutes value or the mean of these three values The strongest correlations were obtained for the mean and the 120 minute values ($R = -0\,62$ and $R = -0\,61$ respectively, $P < 0\,001$) A WHO expert committee (1965) has recommended the following capillary true blood sugar levels at 120 minutes as diagnostic diabetic 140 mg and over per 100 ml borderline 120 to 139 mg per 100 ml and normal less than 120 mg per 100 ml Using these criteria a comparison with the IVGT was made as shown in table 11 Full accordance between the results of the two tests was obtained in 47 per cent of the patients Some discordance is to be expected due to individual variation in glucose tolerance Also they do not measure identical parameters

Table 11 *Glucose tolerance determined with oral (OGT) and intravenous (IVGT) methods in 43 patients with ID*

OGT	IVGT			Total
	Diabetic	Borderline	Normal	
Diabetic	6	4	1	11
Borderline	5	3	[illegible]	12
Normal	1	6	13	20
Total	12	11	20	43

of carbohydrate metabolism as e g after oral glucose administration factors such as the emptying *rate of the stomach* (Nisell 1957) intestinal absorption and possibly gastrointestinal hormones (Mc Intyre et al 1965 Pfeiffer et al 1965) influence the results In spite of this only 2 out of the 43 patients showed fully *discordant results* and most of the overlapping occurred in the borderline groups as could be expected 30 per cent of the patients were normal according to both tests as compared to 47 per cent for each test separately

Few comparisons between the IVGT and OGT in the same subjects have been presented Lundbaek (1960) obtained correlations between the k value and both the 180 minute blood glucose value and the per cent fall of blood glucose from the maximum value to 180 minutes in 45 diabetics Nadon *et al* (1964) compared OGT with IVGT determined according to Amatuzio et al (1953) wherefore detailed comparisons with the present study are difficult to make but their results seem to be in accordance It appears that their *correlation* between the k value and the 120 minute blood glucose value corresponds well to that of the present study

The constant finding of low glucose tolerance in patients with ID as reported by others as well as by myself lessens the probability of this being due to selection The results obtained in the populations of *Tecumseh (Ostrander* et al 1965) and Bedford (Keen et al 1965) as regards the association between carbohydrate metabolism and the prevalence of cardiovascular disease lend further support to the validity of the above results

In the epidemiological study *from* Tecumseh Ostrander et al (1965) *found* that the proportion of elevated blood glucose levels defined as belonging to the upper quintile of the blood *glucose levels* obtained 1 hour after the *ingestion* of 100 g of glucose was significantly *higher for* the participants with cardiovascular disease than for those without The *results* of Epstein et al (1965) *from* the same study *suggested that* hyperglycemia was an independent *risk factor* among persons with coronary heart disease in Tecumseh and seemed to be at least as *important* as either

hypertension or hypercholesterolemia In a sample from the population of Bedford (Keen et al 1965) the participants were classified as diabetic, borderline, and normal according to their blood sugar level 2 hours after 50 g of glucose per mouth The age adjusted prevalence of both symptoms and electrocardiographic changes of arterial disease was lowest in the control group, intermediate in the borderline group and highest in the diabetics In these studies an association between carbohydrate metabolism and ID was obtained with glucose tolerance as the basis, whereas in the other studies above as well as in my own the basis was ID

It has thus been found that a relation of low glucose tolerance to ID exists in populations as well as in selections of patients in different countries and irrespective of methods

Clinical diabetes

During the present study 24 patients with a first myocardial infarction and clinical diabetes otherwise fullfilled the criteria for inclusion under A 1 As was discussed under Material another 10 non diabetic patients had accidentally been omitted from this group but there is no reason to assume that their glucose tolerance differed from that of the patients included 60 per cent of the 190 patients under A 1 had diabetic or borderline IVGT which means that the ratio of clinical diabetics to patients with low IVGT can be estimated to 1 5 According to a sample from the Birmingham survey (Report of a working party appointed by the College of General Practitioners 1963) the ratio between florid diabetes and GTT (glucose tolerance test) diabetes was also 1 5 These similar ratios are thought to be worth mentioning but as they may be coincidental they do not warrant further conclusions regarding similarities in the disposition to ID in clinical diabetes and low IVGT

Age

In the patients with ID, as well as in the controls a weak correlation between increasing age and decreasing IVGT was obtained which in the patients under A 1 and in the controls was dependent on the results in those aged 70 or more The higher frequencies of diabetic and borderline IVGTTs in these ages were of small importance for the overall results, as such patients only comprise 15 per cent of the total number under A The ages of the controls (mean 57 range 32 to 89 years) and the patients with ID (mean 59 range 33 to 85 years) were not matched but the difference in IVGT between the two groups was not due to discrepancies as to age as this difference remained on comparison of corresponding age groups

As regards the relation between age and IVGT in ID the results of Boehle & Schrade (1960) were similar to those of the present study On the other hand Reaven et al (1963) obtained no such correlation nor did Aleksandrow (1962) This reflects the weak correlation the demonstration of which requires a large number of subjects

Sex

The males and the females under A 1 had similar IVGT but not those under A 2—4 The reason for this discrepancy is not clear and may be an effect of selection One possible explanation may be that the mean age of the females in the former group was 6 years higher than that of the males as compared to 2 years in the latter

group but with the low grade correlation between age and IVGTT thus is unlikely Neither Reaven et al (1963) nor Nye (1964) obtained sex differences as regards OGT in ID Nor could such a difference be obtained in the controls and the problem was also discussed in Chapter V The results obtained by others and myself suggest no great if any differences in glucose tolerance between the sexes

Diabetic heredity

Diabetic heredity was not related to IVGT in the patients with ID nor in the controls The results of Reaven et al (1963) are inconclusive as he only had 6 patients with ID and diabetic heredity Referring to the discussion in the foregoing chapter the possibility of an association of diabetic heredity to low glucose tolerance remains to be elucidated

Obesity and hypertension

Obesity was related to low IVGT in the patients under A 1 and A 2—4 but not in the controls The reason for this discrepancy is not known but the explanation could be that obesity and low IVGT are interdependently associated with the development of ID Anyhow these findings do not elucidate the problem as to the relation between obesity and IVGT Low glucose tolerance in obese subjects with ID was also found by Boehle & Schrade (1960) and Aleksandrow et al (1967) but not by Reaven et al (1963) In the present study the age distribution of the obese patients was the same as that of the non-obese wherefore the low glucose tolerance of the former was not the result of a high incidence of obesity among the elderly patients The relation of obesity to low IVGT was not affected by the presence of either diabetic heredity or hypertension On the other hand Drazin (1953), using an OGTT concluded that where obesity and hypertension coexist decreased glucose tolerance occurs more frequently Unfortunately he gives no information regarding the presence of ID among his patients Hypertension was of no influence on the IVGT in the present study nor in that of Reaven et al (1963) Also Epstein et al (1965) found that hyperglycemia was a risk factor among persons with coronary heart disease independent of blood pressure or serum cholesterol This independent association of hyperglycemia with ID was of further interest as the patients under A 1 in the present study who had neither diabetic heredity obesity hypertension nor signs of cardiovascular disease preceding the myocardial infarction, had the same IVGT as the remaining patients in this group

Fasting blood glucose

In the patients under A 1 and A 2—4 the fasting blood glucose level was correlated to the k value (R = —0 41 and R = —0 25 respectively) This correlation did not change essentially on subsequent tests in those under A 1 In the controls the corresponding correlation was weaker (R = —0 12) which partly may be due to a different distribution of k values The association of IVGT and ID was not reflected by the fasting blood glucose levels as the mean value of the patients with ID was 82 mg per 100 ml as compared to 83 mg per 100 ml of the controls Fasting blood glucose levels within the so called normal ranges are thus of low predictability as regards the IVGT and are furthermore of different significance in ID and in controls 59 per cent

of the patients with ID and fasting blood glucose 70 to 89 mg per 100 ml had diabetic or borderline k values as compared to 12 per cent of the controls, and for fasting blood glucose 90 mg per 100 ml or more the corresponding figures were 85 and 23 per cent respectively. Fasting blood glucose levels of 110 mg per 100 ml or more were diagnostic of diabetic IVGT in the present study. Between 100 to 109 mg per 100 ml 2 out of 12 patients with ID and 3 out of 5 controls had normal k values.

Effect of acute myocardial infarction

In myocardial infarction hyperglycemia is often noted during the first days after the acute episode. Its significance is obscure and has caused much speculation (Levine & Brown 1929, Edelmann 1934, Raab & Rabinowitz 1936, Goldberger et al 1945). If this acute condition is accompanied by a temporary change of IVGT it must be of short duration according to the present results, as the patients tested 3 to 7 days after admission had the same IVGT 3 to 6 weeks later. No was the observation of glucosuria during the first days of hospitalisation predictive of low IVGT. The urine sampling was not carried out uniformly, but as these inconsistencies occurred randomly they should not affect this finding but they may explain the rather low frequency, 15 per cent, of glucosuria noted. On the contrary Frehner & Wegmann (1963) obtained signs of latent diabetes in 7 out of 9 patients with glucosuria after the acute myocardial infarction at glucose tolerance tests 5 weeks after the acute episode, as compared to 4 out of 18 patients without glucosuria.

Physical inactivity

Physical inactivity has been stated to be followed by decreased glucose tolerance (Blotner 1945), but no conclusive evidence has been presented. ID is associated with a varying limitation of physical activity. This has probably not been of importance in the present study as the IVGT has been determined in the patients when confined to bed while hospitalised and after hospitalisation when many have been well rehabilitated and in good physical condition, with no differences in the results. Also 50 per cent of the patients under A 1 had the myocardial infarction as the first sign of ID but had the same IVGT as the remaining patients, who had previously experienced some physical incapacitation.

Diuretics

During these last years diuretics such as thiazides and chlorthalidone have been found to aggravate diabetes mellitus (Goldner et al 1960), mild diabetes (Runyan 1962) and to provoke hyperglycemia in patients with hypertension and potential diabetes (Shapiro et al 1961) and in apparently non diabetic patients with hypertension (Wolff et al 1963). Treatment with such diuretics was of no influence on the results in the present study, but this does not exclude a diabetogenic effect of these drugs after long term administration in patients with ID as the medication had been of short duration in many of the patients.

Insulin sensitivity

In a sample of patients with ID there was a correlation between the IVGT and the intravenous insulin sensitivity (IS) at 10, 20 and 30 minutes after the injection of insulin. Accordant results were obtained by Waddell & Field (1960) whose subjects with ID had a relative unresponsiveness to hyperglycemia after oral glucose oral glu

cose loading and to the hypoglycemia 20 minutes after the intravenous injection of 0.1 IE insulin per kg bodyweight. The significance of the relation between these parameters of carbohydrate metabolism is not known.

Variation of IVGT

The individual variation of the k value, even if at times rather great numerically, seldom caused a change in classification of any practical importance. Of the retested patients in table 8 only 6 per cent of those with initially diabetic k values were normal at the retest, and 10 per cent of the initially normal patients had become diabetic. The designation borderline to k values ranging 0.91 to 1.10 appears motivated, as about the same number of patients with such initial k values have since become diabetic as have become normal.

It was not possible to follow the IVGT of the patients with ID uniformly throughout the present study. From the beginning I tried to retest all of those living in Stockholm at least once yearly, but owing to their increasing numbers most efforts to do this had to be concentrated on those under A 1. Since the beginning of 1963 these patients have been tested routinely twice before leaving the hospital, 6 months later and from then on once yearly. Otherwise retesting has been undertaken randomly.

The IVGT of the patients with ID did not change significantly with time in the present study with reference to the results obtained 3 to 6 weeks after the acute myocardial infarction. Therefore the low IVGT often met with in ID should be regarded as a chronic state and not as a temporary abnormality.

Clinical diabetes

The predictive value of glucose tolerance tests concerning the development of clinical diabetes is of great interest. Unfortunately the results of the present study do not supply much information concerning this, owing to the irregular follow up of the patients. Also survivors from myocardial infarction offer no ideal group for these purposes, as their long term mortality rates are relatively high. The combination of low IVGT with high fasting blood glucose levels and/or obesity was not surprisingly the common feature in those 6 patients who developed clinical diabetes, 3 of whom also had diabetic heredity. None of the patients with initially normal IVGT is known to have developed clinical diabetes.

One of the above mentioned 6 patients belonging to A 1 also had a retinopathy suggestive of diabetes at the last control. Such abnormalities were not detected in any other patient, which is probably to be expected, as they occur but rarely in the absence of clinical diabetes.

Prognostic implication of IVGT

Long term survival in relation to IVGT was studied in the patients under A 1, who for this purpose were classified according to their k values represented in fig. 1. To evaluate the prognostic implication of IVGT the patients with diabetic and borderline k values were considered as comprising one group with low IVGT for reasons given under Results. At the last follow up 12 per cent of the patients with normal IVGT were dead as compared to 27 per cent of those with low IVGT, the difference being significant. For these groups the observation months of the patients as alive or dead also

of the patients with ID and fasting blood glucose 70 to 89 mg per 100 ml had diabetic or borderline k values as compared to 12 per cent of the controls and for fasting blood glucose 90 mg per 100 ml or more the corresponding figures were 85 and 23 per cent respectively Fasting blood glucose levels of 110 mg per 100 ml or more were diagnostic of diabetic IVGT in the present study Between 100 to 109 mg per 100 ml 2 out of 12 patients with ID and 3 out of 5 controls had normal k values

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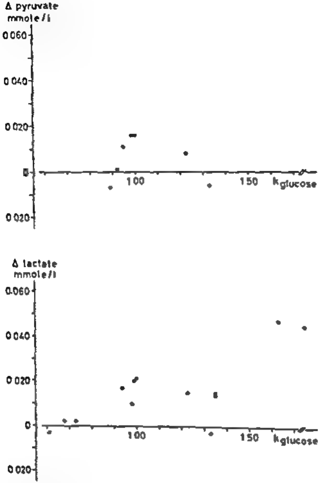


Fig. 1. The relation of blood pyruvate and lactate at 30 minutes as difference from fasting levels in mmole/l to the k value of the IVGTT

Further observations on the low IVGT in ID

Clinical diabetes is a complex metabolic syndrome which is primarily characterised by low glucose tolerance and carries a high morbidity in vascular disease. The relation between clinical diabetes and low IVGT as in the present study is not well known but is of great importance for the concept of diabetes. The low IVGT encountered in ID was chronic and related to oral glucose tolerance as well as to intravenous insulin sensitivity and in order to find out if this low IVGT also correlates to further parameters of carbohydrate metabolism in a way suggestive of clinical diabetes the following studies were undertaken.

Hagenfeldt & Wahlberg (1966, to be published) investigated the *relation of the IVGT to the intravenous tolbutamide*

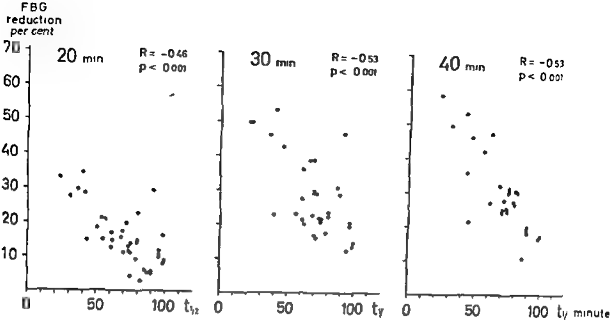
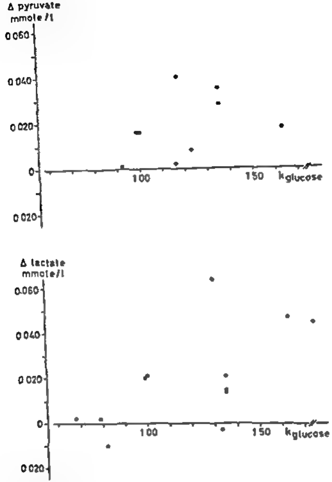


Fig 20 The relation of the intravenous tolbutamide response at 20 30 and 40 minutes as reduction per cent of fasting blood glucose to the half life of blood glucose during the IVGTT

differed correspondingly If the patients *with borderline IVGT* are excluded on account of being an intermediate group the difference as regards long term survival be tween those with normal and those with diabetic IVGT becomes more pronounced than that given above the over all mortality in the latter patients amounting to 58 per cent

The mean age of the patients with low *IVGT* was 3 years higher than that of the patients with normal IVGT but the above differences in mortality rates can only to a small extent be caused by age differences After dividing the patients into two groups one aged 39 to 69 years and the other 70 years or more the differences in the mean ages for those with low and normal IVGT was reduced to 1 year in both age groups but the differences in the mortality rates for the patients with low and normal IVGT remained similar to those obtained before this subdivision The small number of patients did not allow statistical analysis of the prognostic significance of IVGT after further subgrouping by age

Studies for comparison are unfortunately not available and at present it seems that few if any risk factors are known regarding long term survival after myocardial infarction (Biörck et al 1958 Sievers 1963) As regards diabetes mellitus Sievers (1963) concluded that the diabetic patients did *not have a worse long term outcome than* could be expected from their having diabetes in addition to myocardial infarction The unfavourable implication of low IVGT on the long term prognosis for survivors from a first myocardial infarction in the present study is therefore of great clinical importance and will be further elucidated by continued follow up and an increase in the number of patients Antidiabetic treatment is of benefit in clinical diabetes and it is possible that such treatment could be of value also in ID



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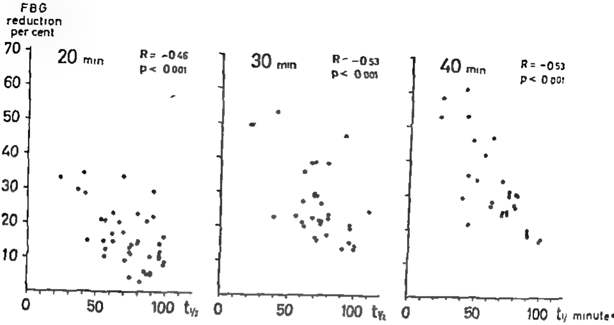

Fig. 20. The relation of the intravenous tolbutamide response at 20, 30 and 40 minutes as reduction per cent of fasting blood glucose to the half life of blood glucose during the IVGTT.

differed correspondingly. If the patients with borderline IVGT are excluded on account of being an intermediate group, the difference as regards long term survival between those with normal and those with *diabetic IVGT becomes more pronounced* than that given above, the over all mortality in the latter patients amounting to 38 per cent.

The mean age of the patients with low IVGT was 3 years higher than that of the patients with normal IVGT, but the above differences in mortality rates can only to a small extent be caused by age differences. After dividing the patients into two groups, one aged 39 to 69 years and the other 70 years or more, the differences in the mean ages for those with low and normal IVGT was reduced to 1 year in both age groups, but the differences in the mortality rates for the patients with low and normal IVGT remained similar to those obtained before this subdivision. The small number of patients did not allow statistical analysis of the prognostic significance of IVGT after further subgrouping by age.

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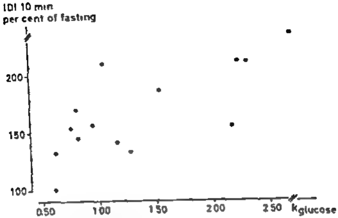

Fig 23 The relation of immunologically detectable insulin (IDI) at 10 minutes as per cent of fasting level to the k value of the IVGTT

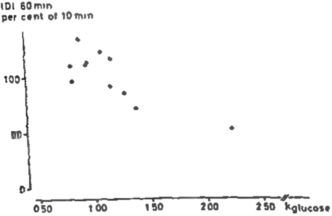

Fig 24 The relation of immunologically detectable insulin (IDI) at 60 minutes as per cent of the 10 minutes level to the k value of the IVGTT

diabetes can be explained by their differing fasting blood glucose levels these being 85 and 168 mg per 100 ml respectively (P < 0 001)

Cerasi & Wahlberg (1966 to be published) investigated *immunologically detectable insulin* (IDI) (Hales & Randle 1963) in fasting and at 10 and 60 minutes during the IVGTT in 26 patients under A The relation between IDI at 10 minutes as per cent of fasting level and the k value is shown in fig 23 the variables being rank

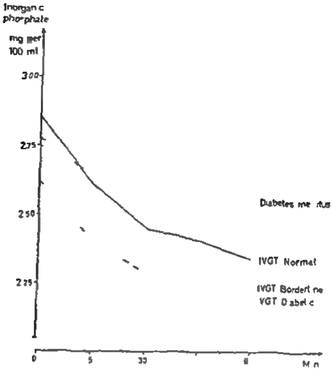

Fig 22 Blood inorganic phosphate in mg per 100 ml during the IVGTT in diabetes and patients with ID classified according to their IVGT

response (Unger & Madison 1958) in 60 of the patients under A The relations of the blood glucose half life in minutes to the per cent reduction of fasting blood glucose at 20 30 and 40 minutes after the injection of tolbutamide are shown in fig 20 Negative rank correlations were obtained at these observation times ($R = -0\ 46$ $P < 0\ 001$ $R = -0\ 53$ $P < 0\ 001$ and $R = -0\ 53$ $P < 0\ 001$ respectively)

Hagenfeldt & Wahlberg (1966 to be published) also studied *blood pyruvate and lactate* (Biochemia Boehringer) *during the IVGTT* in 31 of the patients under A The relations between the k value and the absolute changes in pyruvate and lactate respectively at 30 minutes are shown in fig 21 at which observation times rank correlations were obtained ($R = 0\ 44$ $0\ 02 > P > 0\ 01$ and $R = 0\ 46$ $0\ 02 > P > 0\ 01$ respectively) *Blood inorganic phosphate* (Gottfried & Erdman 1951) *during the IVGTT* was studied in another 44 patients under A and in 18 clinical diabetics under C and the results are shown in fig 22 No association between the IVGT and the changes in inorganic phosphate was obtained in the patients with ID and these patients lowered their inorganic phosphate significantly more than those with clinical diabetes ($P<0\ 01$ at all observation times) On the other hand a negative rank correlation was obtained between fasting blood glucose and the change in inorganic phosphate at 15 and 30 minutes ($R = -0\ 35$ $0\ 0? > P > 0\ 01$ and $R = -0\ 32$ $0\ 02 > P > 0\ 01$ respectively) for the total number of subjects Therefore the difference in changes of inorganic phosphate between the patients with ID and those with clinical

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VII

SERUM LIPIDS INTRAVENOUS GLUCOSE TOLERANCE AND THEIR RELATIONSHIP STUDIED IN ISCHAEMIC DISEASE

by

Lars A Carlson and *Fredrik Wahlberg*

In so called ischaemic disease such as myocardial infarction angina pectoris and intermittent claudication the serum lipids as well as the glucose tolerance are often abnormal The concentration of cholesterol and or triglycerides in serum may be elevated (2 3 5 8 13) and the oral (6 19 21) as well as the intravenous (23) glucose tolerance may be reduced Furthermore several reports have demonstrated various derangements of carbohydrate metabolism in different kinds of hyperlipoproteinemia such as hypercholesterolemia (22) and hypertriglyceridemia (1 12 14 15 17)

This investigation was undertaken to study the relationship between lipid and carbohydrate metabolism in ischaemic diseases as revealed by determination of fasting concentrations of cholesterol and triglycerides in serum and by the intravenous glucose tolerance test (IVGTT) Furthermore an estimate of the frequency of abnormalities of these parameters of lipid and carbohydrate metabolism in ischaemic disease was obtained

Material and methods

For the present study *ischaemic disease* was restricted to myocardial infarction angina pectoris and intermittent claudication All patients with *myocardial infarction* had been hospitalised during their acute illness and presented at least 2 of the 3 following criteria a clinical history ECG and/or transaminase (GOT GPT) changes suggestive of acute myocardial infarction *Angina pectoris* and *intermittent claudication* were diagnosed from a typical history and the latter diagnosis was also confirmed by oscillometry of the legs Accordingly *100 males and 22 females were selected* their serum lipids and IVGT being unknown The male group contained 64 survivors from myocardial infarction 24 patients with angina pectoris and 12 patients with intermittent claudication Corresponding figures for the women were 11 4 and 7 Another 20 male patients were selected on account of the presence of *ischaemic disease as well as hyperlipoproteinemia* the mean age being 53 years 10 of them had survived one or

* Presented in part before the Swedish Society of Internal Medicine in Stockholm, May 1962

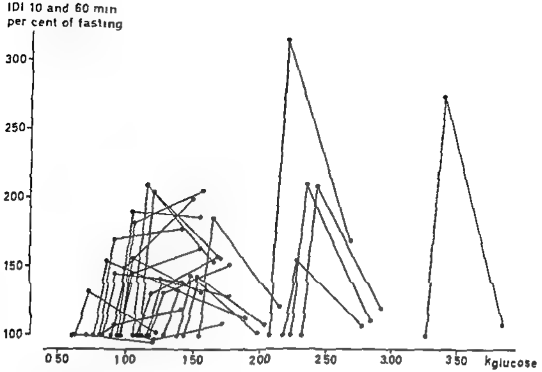

Fig 25 Immunologically detectable insulin (IDI) at 10 and 60 minutes during the IVGTT in per cent of fasting level in relation to the k value of the IVGTT

correlated (R = 0 43, P < 0 05) The relation between IDI at 60 minutes as per cent of the 10 minutes level and the k value is shown in fig 24, the variables being negatively rank correlated (R = −0 65, P < 0 01) The findings are further illustrated in fig 25, where the responses of IDI at 10 and 60 minutes in per cent of the fasting level are shown in relation to the k value

According to these findings no essential differences have been revealed between the low IVGT as in the present study and clinical diabetes as regards their metabolic derangements It would thus appear that the metabolic abnormality producing this low IVGT differs biochemically from clinical diabetes in degree rather than nature However the nature of both conditions remains unknown

Table 1 Age levels of cholesterol and triglycerides in serum and k value for the intravenous glucose tolerance test in 100 men and 22 women with ischaemic disease

	MEN				WOMEN			
	Age years	Cholesterol mg/100 ml	Triglycerides mmole/l	k %/min	Age years	Cholesterol mg/100 ml	Triglycerides mmole/l	k %/min
Mean value	59	290	2 27	1 14	61	94	1 88	1 32
Range	36—78	163—432	0 60—12 0	0 45—2 98	45—76	213—380	0 83—5 92	0 65—2 66

frequent lipid abnormality was elevation of the serum triglycerides only which occurred in 25 men Elevation of serum cholesterol only occurred in 10 men and elevation of both these lipid fractions in 15 A diabetic IVGT was encountered in 33 men and a borderline one in 23

Of the 50 men with normal plasma lipids 31 had borderline or diabetic IVGT which means that *only 19 men of the 100 studied had both serum lipids and IVGT within normal limits*

Of the 22 women with ischaemic disease 11 had some plasma lipid abnormality* and 9 had borderline or diabetic IVGT Of the 11 women with normal plasma lipids 5 had diabetic or borderline IVGT which leaves 6 of the 22 women with normal serum lipids and IVGT

Hyperlipoproteinemia and IVGT

There were no significant differences in the distributions of the k values between the 50 male patients with normal serum lipids and the total group of 50 patients with hyperlipoproteinemia neither on comparisons between the 3 groups with hyperlipoproteinemia (Fig 1) Nor were any significant differences obtained on separate comparison of the patients with normal serum lipids and either the ones with elevated cholesterol only or those with elevation of both cholesterol and triglycerides However the k values of the group with elevated triglycerides only were significantly higher ($P < 0.05$) than those of the group with normal lipids mean k values being 1 30 and 1 03 respectively

The male patients with ischaemic disease and known hyperlipoproteinemia were added to the material above as the result of an increase of the hyperlipemic groups was considered to be of interest in this context Of these 20 patients 7 had elevations of cholesterol only 7 elevations of cholesterol and triglycerides and 6 elevated triglycerides only No significant changes of the above mentioned results with regard to the relationship between hyperlipoproteinemia and IVGT occurred in this pooled group

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* Abnormality according to normal values defined for men (7) In a recent unpublished study (11) we have seen that healthy men and women in Stockholm have fairly similar serum cholesterol levels while the women have significantly lower triglyceride levels

more myocardial infarctions, 7 had angina pectoris, and 3 had intermittent claudication

The material consists of patients who were accessible for study from October 1961 until June 1964 All patients were ambulatory, in good general condition at the time of the study, and there was a minimum interval of 1 month to any previous acute myocardial infarction They were on their ordinary diets and in no case had any dietary prescriptions been made aimed at reducing the blood lipid levels or the weight No patient had a history suggesting diabetes or glucosuria or other disease known to affect carbohydrate metabolism

The patients reported to the laboratory in the morning after fasting over night After a rest in the recumbent position for at least 15 minutes capillary blood samples in duplicate or triplicate were, as subsequently, drawn from the earlobes for glucose determination A needle was then inserted into an ante cubital vein and blood withdrawn for lipid analysis and the intravenous glucose tolerance test (IVGTT) then commenced by injection of 25 grams of glucose in a 60 per cent aqueous solution through the same needle Zero time was set at the end of the injection Capillary blood samples were then taken after 10 and 20 minutes and from then on at every fifth minute until 60 minutes with the samples at 20 and 60 minutes in duplicate (23) The blood glucose values between 20 and 60 minutes form an apparently straight line when plotted against time in a semilogarithmic system (23) By extrapolation of this line the k value for the disappearance of blood glucose in per cent per minute was estimated by graphic methods

The blood withdrawn for lipid analysis was allowed to clot at room temperature for one hour and the serum was then immediately separated off by centrifugation The sera were kept at —14° C until analysed Serum lipids were determined as described earlier (7), cholesterol essentially according to Sperry Webb (20) and triglycerides according to Carlson (10) Blood glucose was determined with glucose oxidase according to Marks (18)

The upper normal limits for serum cholesterol and triglycerides have been set at 322 mg per 100 ml and 2 20 mmole/l respectively according to previously established normal values in healthy men in Stockholm (7) k values 0 90 and lower have been called diabetic, 0 91—1 10 border line and 1 11 and higher normal (23)

Statistical calculations were performed by testing differences between means and distributions according to Wilcoxon and correlations according to Spearman as the parameters studied are not normally distributed

Results

The male and the female groups of patients selected on account of ischaemic disease are characterised with regard to age serum lipid values and k values in table I These variables exhibit a wide range of values and their means do not differ significantly on comparison between the men and the women

Frequency of serum lipid and glucose tolerance abnormalities

The 100 males selected due to the presence of ischaemic disease were grouped according to their serum lipid pattern and k value as shown in Figure 1 50 of them had some plasma lipid abnormality and 56 had borde line or diabetic IVGT The most

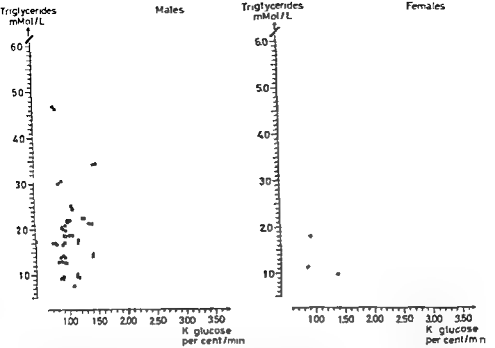


Fig 3 Relationship between the concentration of serum triglycerides and the IVGT (k value) for men (left) and women (right) Closed symbols = Patients selected on account of ischaemic disease Open symbols = Patients selected on account of hyperlipoproteinemia The two highest values for the men were 7 5 and 12 0 mmole/l

Serum cholesterol level and IVGT

The serum cholesterol and the k value are plotted in Figure 2 for the men and the women It is obvious that no relationship existed between serum cholesterol and k value for the men and statistical analysis showed that R<0 16 (P>0 05)

For the women on the contrary the k values increased significantly with increasing concentration of cholesterol in serum The correlation coefficient for the concentration of cholesterol in serum and the k value was R = 0 69 (P<0 01)

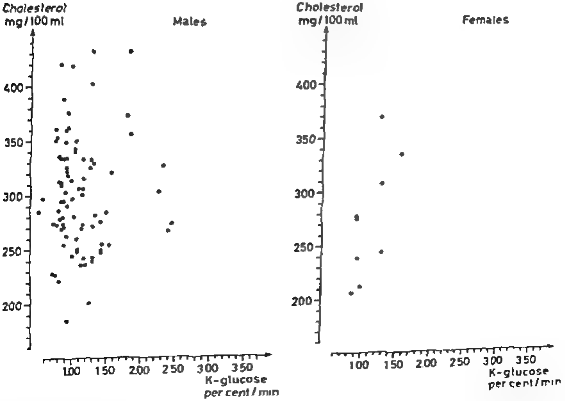
To ascertain if age had any effect on these results the men and the women were divided into subgroups by ages above and below the mean age For the males there was still no correlation between serum cholesterol and k value either for the 48 men below 59 years (R<0 24 P>0 05) or for the 52 men above this age (R<0 23 P>0 05) For the 10 women younger than 61 years the rank correlation coefficient between serum cholesterol and k values was R = 0 68 (P<0 05) and for the 12 older women the corresponding figure was R = 0 71 (P<0 02)

Serum triglyceride level and IVGT

The serum triglycerides and the k values are given for the men and the women in figure 3 No correlation between these two

		Serum Lipids				
	Cholesterol	Normal	Elevated	Elevated	Normal	Total
	Triglycerides	Normal	Normal	Elevated	Elevated	
Intra Venous Glucose Tolerance	Normal	19	6	5	14	44
	Borderline	14	1	3	5	23
	Diabetic	17	3	7	6	33
	Total	50	10	15	25	100

Fig 1 Distribution of 100 male patients with ischaemic disease according to the occurrence of normal or abnormal serum lipids and *IVGT* *The upper normal limit for cholesterol* was *322 mg/100* ml and for triglycerides 2.2 mmole/l (8) Borderline IVGT was defined as $k = 0.91—1.10$ and a diabetic as $k \leq 0.90$ (23)



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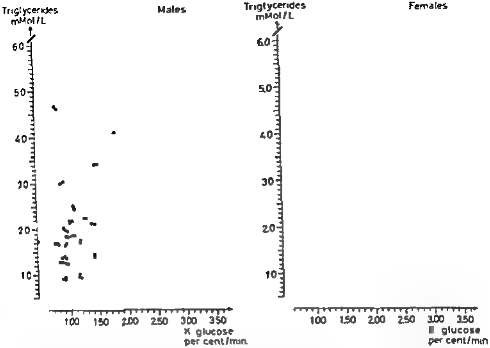

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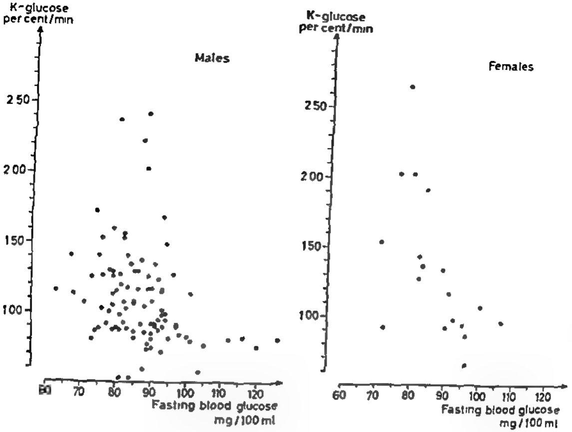

Fig 4 Relationship between the fasting level of blood glucose and the IVGT (k value) in 100 men (left) and 22 women (right) with ischaemic disease

parameters can be seen either for the men ($R<0.17$ $P>0.05$) or for the women ($R<0.36$, $P>0.05$) Nor were any correlations obtained after subdivision of the material by age as described above for cholesterol

Serum lipids and fasting blood glucose levels

The relationship between the fasting blood glucose level and the k value is shown in figure 4 for the males and the females For both sexes there was a significant negative correlation for the males $R = -0.37$ ($P<0.001$) and for the females $R = -0.74$ ($P<0.001$) As there was only a low grade correlation between these two variables for the men it was of interest to study if the fasting level of blood glucose correlated better to the serum lipids than the k value

The relationships between the fasting blood glucose levels and the serum lipids for the men and the women are shown in figures 5 and 6 The only significant correlation was negative and between cholesterol and blood glucose for the women in whom high cholesterol levels were associated with a low concentration of blood glucose ($R = -0.57$ $P<0.05$) This was not unexpected as they had shown fairly strong correlations on the one hand between k value and cholesterol level and on the other hand between k value and fasting blood glucose level

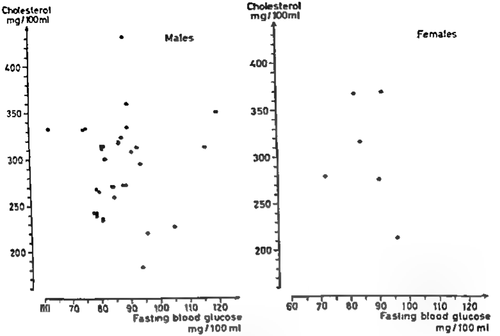

Fig 5 Relationship between the fasting level of blood glucose and the concentration of serum chol s erol in 100 men (left) and 2? women (right) with ischaemic disease

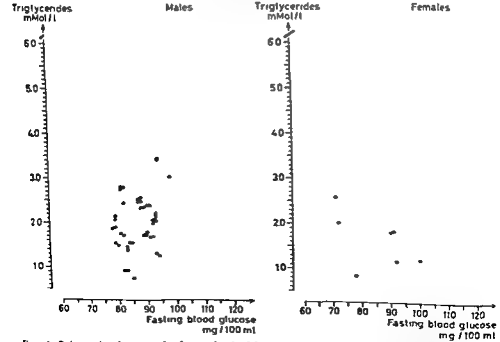

Fig 6 Relationship between the fasting level of blood glucose and the concentration of serum tri glycerides in 100 men (left) and 2 women (right) with ischaemic disease The tw highest values for the en were 7 5 and 1 0 mmole/l

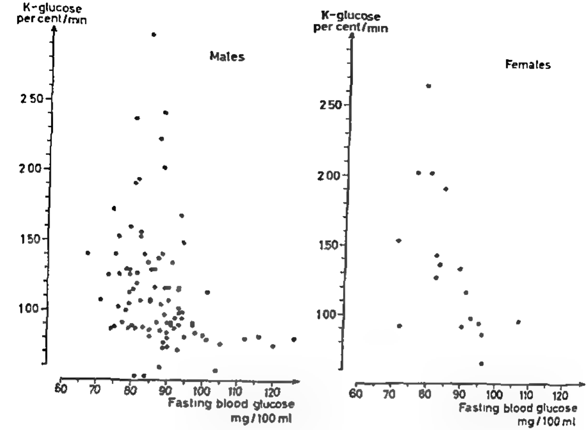

Fig. 4. Relationship between the fasting level of blood glucose and the IVGT (k value) in 100 men (left) and 22 women (right) with ischaemic disease

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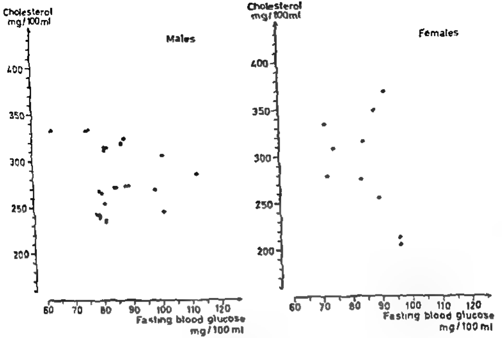

Fig 5 Relationship between the fasting level of blood glucose and the concentration of serum cholesterol in 100 men (left) and 22 women (right) with ischaemic disease

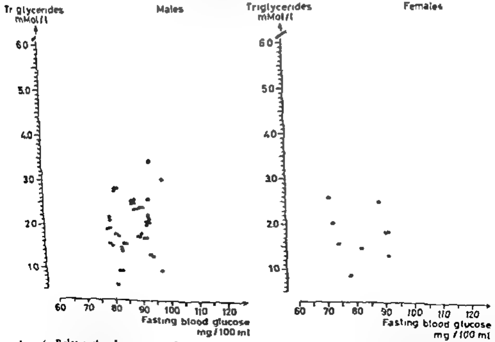

Fig. 6 Relationship between the fasting level of blood glucose and the concentration of serum triglycerides in 100 men (left) and 22 women (right) with ischaemic disease The two highest values for the men were 7 5 and 1[illegible]0 mmole/l

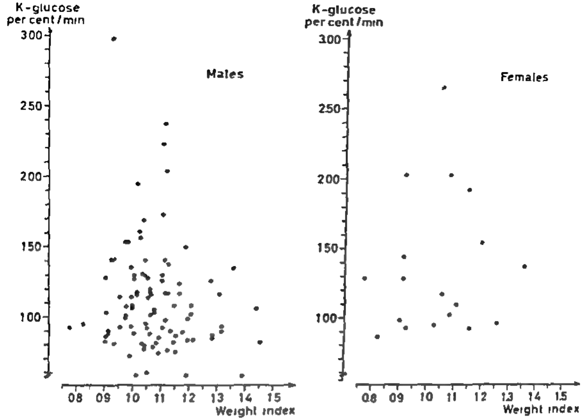

Fig 7 Relationship between the IVGT (k value) and the weight index in 100 men (left) and 22 women (right) with ischaemic disease

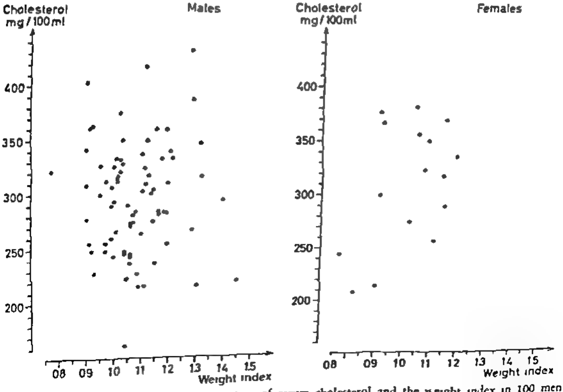

Fig 8 Relationship between the concentration of serum cholesterol and the weight index in 100 men (left) and 22 women (right) with ischaemic disease

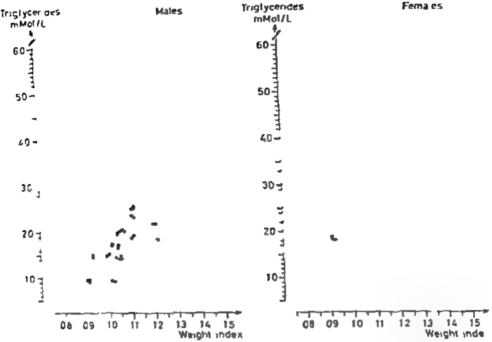

Fig 9 Relationship between the concentration of serum triglycerides and the weight index in 100 men (left) and 22 women (right) with ischaemic disease The two highest value for the men were 7 5 and 1 0 mmole/l

Serum lipids IVGT and weight index

Obesity has been found to be associated with derangements of lipid and carbohydrate metabolism This prompted us to study the relation between weight index obtained as weight of patient/ normal weight (16) and serum cholesterol triglycerides and k value which is illustrated in figures 7 8 and 9 The triglyceride level tended to increase with increasing weight index in men (R = 0 30 P<0 01) otherwise no significant correlations occurred

To evaluate the effect of a high weight index on the relation between serum cholesterol triglycerides and k value the 23 men and the 7 women with a weight index above 1 15 were selected No correlations between the serum lipid levels and the k value were then obtained

Discussion

Several studies on patients with ischaemic disease have dealt with serum lipids and/or glucose tolerance However few studies of ischaemic disease are available in which serum lipids and glucose tolerance have been studied and interrelated in the same patients

In the present study it is of interest to note that about as many patients had some kind of serum lipid abnormality as an abnormally decreased glucose tolerance and

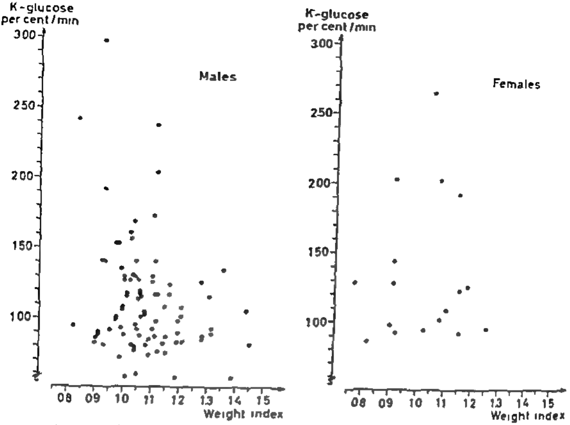

Fig 7 Relationship between the IVGT (k value) and the weight index in 100 men (left) and 22 women (right) with ischaemic disease

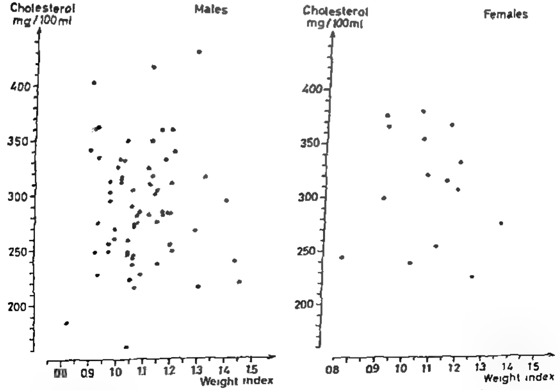

Fig 8 Relationship between the concentration of serum cholesterol and the weight index in 100 men (left) and 22 women (right) with ischaemic disease

general behaviour of the IVGT in hypertriglyceridemia It is possible that this finding is due to that the present study only deals with patients having ischaemic disease

Furthermore in the women the IVGT *increased* with increasing cholesterol levels This contradicts an association between hypercholesterolemia and decreased glucose tolerance at least in patients with ischaemic disease

Summary

The fasting levels of cholesterol and triglycerides in serum and the intravenous glucose tolerance were determined in 100 male and 22 female patients selected on account of ischaemic disease (myocardial infarction angina pectoris intermittent claudication)

Fifty of the men had some kind of serum lipid abnormality hypertriglyceridemia being more common than hypercholesterolemia A borderline or abnormal glucose tolerance was found in 56 of the men Only 19 men had both serum lipids and glucose tolerance within normal limits The figures for the small female group were similar

In the male group there was no tendency for the glucose tolerance to decrease with increasing levels of either cholesterol or triglycerides in serum On the contrary the glucose tolerance was *higher* in the group with elevated triglycerides only than in the group with normal lipids

In the female group the glucose tolerance was positively correlated to the serum cholesterol levels the correlation coefficient between these two parameters being statistically significant

There was a slight positive significant correlation between weight index and triglyceride level for the men

that only around 20 per cent of the patients were normal with regard to *both* serum lipid levels and glucose tolerance In the context of serum lipids, triglyceride abnormalities were more common than cholesterol abnormalities Similar results have been reported in earlier studies in ischaemic diseases (2, 3, 5) It is also interesting to note that the frequency of abnormal serum lipids as well as of abnormal glucose tolerance, is similar to that obtained by Carlson (8) and Wahlberg (23) in earlier, unrelated studies Therefore the results of the present study are thought to be representative of those obtained in similarly selected patients with ischaemic disease

The existence of interrelationships between lipid and carbohydrate metabolism in tissues is well documented Therefore it is not surprising that several authors have looked for certain relationships between serum lipids and glucose tolerance as these parameters might reflect derangements of metabolism on a cellular plane Several studies have been performed on patients selected on account of overt diabetes and major plasma lipid abnormalities such as hypercholesterolemia and hypertriglyceridemia The occurrence of impaired glucose tolerance in idiopathic hyperlipemia was described by Lewer Smith & Hurley in 1954 (17) Adlersberg & Wang reported in 1955 on 5 patients with idiopathic hyperlipemia with mild diabetes mellitus (1) In 20 patients with idiopathic hypercholesterolemia the majority of which had been selected due to the presence of vascular disease Waddell et al found an abnormal oral glucose tolerance in 18 (22) In 14 subjects with marked fasting hypertriglyceridemia Kane et al found that only 3 had normal oral glucose tolerance (14) In patients selected on account of diabetes it is now well established that hypertriglyceridemia is the dominating serum lipid abnormality especially when the control of carbohydrate metabolism is poor (9)

In this study, however, we could not demonstrate any relationship between high serum lipid levels and low glucose tolerance There was furthermore no increase in the frequency of abnormal IVGTTs even in the patients with the most excessive lipid abnormalities For example 2 of the 5 male patients with cholesterol above 400 mg per 100 ml plasma had a k value below 1 10 while the corresponding figures for the patients with cholesterol below 220 were 3 of 6 Similarly 2 of 5 male patients with triglycerides above 5 mmole/l had a k value below 1 10 while the same figures in patients with triglycerides below 1 mmole/l were 5 of 10 Apparently the frequency of abnormal k values does not vary with the serum levels of either cholesterol or triglycerides in the present material of patients with ischaemic disease Similar results were obtained by Reaven et al (19) They found that a group of 41 patients with myocardial infarction had a reduced oral glucose tolerance when compared to a control group of patients without coronary artery disease The levels of cholesterol and triglycerides in plasma were also elevated However they could not find any statistically significant relationship between carbohydrate intolerance and hyperlipemia Their results are thus on a par with our findings in the present material of 100 patients with ischaemic disease The fact that in our patients the IVGT was indeed higher in the group with elevated serum triglycerides only than in the group with normal serum lipids should not be taken as a reflection of the

general behaviour of the IVGT in hypertriglyceridemia It is possible that this finding is due to that the present study only deals with patients having ischaemic disease

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SUMMARY AND CONCLUSIONS

I The aim of the present investigation was to study intravenous glucose tolerance (IVGT) in ischaemic cardiovascular disease (ID) manifested by myocardial infarction angina pectoris and intermittent claudication

II The metabolic pathways leading to ID are unknown but it has been found that the development and clinical manifestations of ID are associated with high frequencies of elevated serum lipid levels as well as with an overrepresentation of clinical diabetes mellitus ID in clinical diabetes is apparently not related to the chemical severity of diabetes as measured by hyperglycemia need of insulin or tendency to keto-acidosis Therefore it was considered possible that abnormal carbohydrate metabolism as revealed by a low IVGT only could be related to ID as well as is clinical diabetes

III Carbohydrate metabolism in ID has previously been studied mostly with oral glucose tolerance tests and high frequencies of abnormal results have been obtained The interpretations of this finding have been diverging and several problems as regards glucose tolerance in ID remain This motivated an investigation of IVGT in myocardial infarction angina pectoris and intermittent claudication Furthermore attempts to assess the role and nature of IVGT in these conditions were undertaken

IV 530 *patients with ID* were investigated They were divided into 4 groups referred to as *A 1—4*

A 1 consisted of *190 survivors from a first myocardial infarction* admitted acutely to the Seraphimer Hospital during the time of the present study November 1960—November 1965

A 2 consisted of *160 survivors from one or more myocardial infarctions* whose first myocardial infarction had not been treated at the Seraphimer Hospital during the time of the present study

A 3 consisted of *120 patients with angina pectoris* without signs of a previous myocardial infarction

A 4 consisted of *60 patients with intermittent claudication* without a history of angina pectoris or signs of a previous myocardial infarction

B 200 subjects without a history or physical signs of cardiovascular disease and with a normal ECG at rest served [illegible] *controls*

C 80 patients with clinical diabetes mellitus were included in order to define diabetic IVGT

V The *IVGT* was tested with a single load of 25 g of glucose injected in 2—4 minutes The result was expressed as a k value representing the per cent per minute reduction of blood glucose During the hyperglycemia approximately between 20 and 60 minutes after the glucose loading the logarithms of the blood glucose values form an apparently straight line when plotted against time and the linearity of this regression function was not disproved on statistical analysis Blood glucose half life was determined graphically by extrapolation of this line and the k value was calculated according to the formula 0 693 100 $t\frac{1}{2}$ The methodological error involved in

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determining k values by this way was found to be without practical importance The k values are somewhat dependent on the glucose dose as the k values after 50 g of glucose were significantly higher than those after 25 g of glucose On the other hand weight differences exceeding 20 kg in otherwise matched subjects were of no influence on the k values after 25 g of glucose Therefore it seems improbable that an adjustment of the glucose dose to body weight would result in k values essentially different from those obtained with a uniform 25 g dose

VI In the present study k values 0 90 and lower were classified as diabetic, k values 0 91 to 1 10 as borderline and k values 1 11 and higher as non diabetic or normal The mean k value of the 80 patients with *clinical diabetes* was 0 57, range 0 19 to 1 03 3 patients having k values higher than 0 90 These results agree with those obtained by other authors and k values 0 91 or higher could be estimated to occur in 7 per cent of patients diagnosed as diabetics, and k values 1 11 or higher in 0 5 per cent, wherefore the above classification is considered valid

VII In the *controls* the mean k value was 1 53, range 0 66 to 3 85 The k values were diabetic in 4 per cent, borderline in 10 per cent and normal in 86 per cent A correlation was obtained between increasing age and decreasing k values which was mainly due to a relative scarcity of high normal k values in the elderly subjects A correlation was also obtained between increasing fasting blood glucose levels and decreasing k values Sex, diabetic heredity obesity, and hypertension were of no influence on the results

The summarised k values from other studies comprising all in all 443 subjects described as non diabetic, healthy, normal or with a diagnosis not indicating cardiovascular disease were estimated to be diabetic in 5 per cent, borderline in 9 per cent, and normal in 86 per cent These results are almost identical with those of the present study, and they are probably representative of those obtained in non diabetic subjects without diagnosed cardiovascular disease

VII In the *530 patients with ID* the mean k value was 1 17, range 0 47 to 4 80 The k values were diabetic in 31 per cent, borderline in 25 per cent, and normal in 44 per cent The mean k values of the subgroups A 1—4 were 1 10, 1 19, 1 25, and 1 15 respectively, no differences being significant The distributions of the k values in the total group and in each of the subgroups all differed significantly from that of the control group Selection and duration of ID did not influence the results in groups A 2—4

Increasing age was correlated to decreasing IVGT, and the obese patients had significantly lower k values than the non obese The males and the females under A 1 did not differ significantly as regards their IVGT, but in those under A 2—4 significant differences were obtained the mean k values of the latter being 1 18 and 1 40 respectively Diabetic heredity and hypertension were of no influence on the results

Increasing fasting blood glucose levels were correlated to decreasing k values At corresponding fasting blood glucose levels the patients with ID had lower IVGT than the controls, their fasting blood glucose levels not differing significantly Fasting blood glucose lower than 100 mg per 100 ml was of low predictability as regards IVGT

No effect of the acute myocardial infarction on the IVGT could be demonstrated in the patients under A 1 Nor was the finding of glucosuria during the first days of hospitalisation predictive of IVGT in these patients

Oral glucose tolerance as well as intravenous insulin sensitivity were correlated to IVGT in samples of patients with ID

The variation of the IVGT was studied over intervals ranging from 1 month to more than 24 months and no significant changes were found to occur 129 of the 190 patients under A 1 had been retested after hospitalisation 6 per cent of the patients with initially diabetic k values had become normal at their latest retest and 10 per cent of the initially normal patients had become diabetic

Clinical diabetes was known to have developed after hospitalisation in 6 patients 5 of whom with initially diabetic k values and 1 with a borderline k value 1 of these patients also had a retinopathy suggestive of diabetes

The patients under A 1 with initially diabetic and borderline IVGT had higher long term mortality rates than those with normal IVGT

IX Fasting serum cholesterol and triglyceride levels were studied in males and females with ID under A 50 per cent of the males had elevated levels of one or both of these lipids 19 per cent of the males had both serum lipids and IVGT within normal limits Corresponding results were obtained in the females The males with elevated triglycerides only had higher k values than those with normal lipids and in the females serum cholesterol was correlated to IVGT Otherwise no relationships between serum lipids and IVGT occurred

X The results of other studies and the present one have shown that ID is associated with low glucose tolerance as measured by either oral or intravenous methods In the present study the low IVGT reflected a chronic state and implied an unfavourable prognosis as regards long term survival after a first myocardial infarction

The IVGT was correlated to oral glucose tolerance intravenous insulin sensitivity intravenous tolbutamide response and to the changes of blood pyruvate lactate and immunologically detectable insulin during the intravenous glucose tolerance test According to these findings no essential differences have been revealed between low glucose tolerance as in the present study and clinical diabetes as regards their metabolic derangements

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ANEMIA IN RHEUMATOID ARTHRITIS

by

OLLE STRANDBERG

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To my wife

Tryckeri Balder AB Stockholm 19[illegible]

CONTENTS

INTRODUCTION

The pathogenesis of the anemia of rheumatoid arthritis has been much discussed and the fact that the extensive literature in this field is still growing serves to indicate that the problems are still far from being solved. The anemia problem has been dealt with from many different aspects, some of the main lines of research having been frequency, morphology, iron metabolism and therapy.

The incidence of anemia among patients with rheumatoid arthritis has been reported by Nilsson (29) as 63 per cent for women and [illegible] per cent for men; some of the patients studied, however, had pelvospondylitis and seronegative arthritis and would not nowadays, with modern serological techniques and diagnostic criteria, be classified as rheumatoid arthritis. Almost identical percentages have been reported by Alexander & Duthie (2) for 2,595 patients with rheumatoid arthritis, though without any diagnostic details being given. The Empire Rheumatism Council (11) has also reported a substantially higher incidence of anemia in women than in men with rheumatoid arthritis.

Morphologically, the anemia is characterised as moderately hypochromic and normocytic. There is fairly good agreement on this point between a relatively large number of reports (17, 29, 39), while Jeffrey (22) and Richmond & al. (33) report a more substantial drop in the erythrocyte indices. It has frequently been pointed out that this anemia displays great morphological and therapeutic similarities with that found in patients with infections (e.g. 6).

A disturbed iron metabolism has been studied from different approaches. The absorption of iron from the gastrointestinal tract in patients with rheumatoid arthritis has been investigated by means of oral iron tolerance tests (22, 29, 40) and radioiron techniques (14, 23, 31, 36, 37). Erythrokinetic examinations have indicated that injected iron is eliminated more rapidly from the plasma space in patients with rheumatoid arthritis than in healthy persons (9, 17, 29, 40).

From the therapeutic angle, several investigators have noted that the anemia is refractory to oral iron (7, 21, 22, 29, 39, 42). A number of research groups tried administering iron saccharate intravenously (21, 34, 39, 42) and were able to correct any iron deficiency found in the arthritis patients; however, the therapy could not eliminate the anemia per se.

A possible cause of the anemia that has been discussed and investigated in recent years is chronic bleeding from the gastrointestinal tract as a result of prolonged ingestion of salicylates (30, 41, 44, 45). Moderate gastrointestinal hemorrhage induced by salicylates was found in approximately 60—70 per cent of cases with rheumatoid arthritis, using either the benzidine test (44, 45) or autologous erythrocytes tagged with Cr^{51} (30, 41). Only in isolated cases were these hemorrhages regarded as being conducive to anemia, nor did any of

with rheumatoid arthritis The data obtained have also been related to body parameters

5 Abnormalities in the serum proteins have frequently been reported in patients with rheumatoid arthritis (for references see 19) the primary finding being low serum albumin concentrations with some tendency to decrease with increasing clinical activity of the disease (43) Attempts have been made to correlate the decrease in albumin and other changes in serum proteins to hematological data and clinical activity

6 Patients with active rheumatoid arthritis have hypoalbuminemia (19) and hypotransferrinemia (25) The metabolism of radio iodine labelled transferrin and albumin has therefore been studied in patients with rheumatoid arthritis and in controls in order to establish whether the reduced concentrations could be ascribed to a retarded or accelerated metabolism of these proteins in patients with rheumatoid arthritis

7 Corticosteroids have been shown to affect the anemia of rheumatoid arthritis (10 12 13 15 20) and some effect on the iron metabolism has also been demonstrated (9) Accordingly a study has been made of the influence of therapeutic doses of corticosteroids on hematological values iron absorption iron utilization by erythrocytes and storage iron in the bone marrow in patients with rheumatoid arthritis

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Several investigators have compared the clinical activity of the rheumatoid arthritis with the hematological findings (22, 23 24 29) and have consistently found that the anemia increases with the clinical activity

There are thus some problems in the anemia of rheumatoid arthritis which are unsettled as outlined above; the present study concerns the following points

1 What picture does one obtain of the anemia of rheumatoid arthritis if cases are classified by diagnostic criteria (3 4) and serological techniques (the rheumatoid factor) with the exclusion of hemorrhagic anemia (salicylates steroid and phenylbutazone induced ulcers)? Hematological laboratory findings have also been studied and correlated to the clinical activity of the disease

2 Possible explanations for the hypoferremia regularly found in patients with active rheumatoid arthritis include the presence of a hyperactive reticuloendothelial system with trapping of iron absorbed from the gastrointestinal tract (18) or defective release of iron from reticuloendothelial cells (17), or defective absorption of iron as judged from flat iron tolerance curves and preliminary tests with Fe^{59} absorption (14)

This problem has been studied in patients with rheumatoid arthritis patients with iron deficiency anemia and in normal cases using oral iron tolerance tests absorption tests with Fe^{59} and from the utilization of Fe^{59} in erythrocytes

3 Conflicting data have been published concerning the utilization of iron in circulating erythrocytes with the iron administered orally (22, 23) or intravenously (9 17). A comparative study has been made of the utilization of a low molecular radioactive iron preparation (iron sorbitol) administered intramuscularly to a group of patients with rheumatoid arthritis and a group of controls. External measurements of radioactivity have also been made to investigate the incorporation in and mobilisation from bone marrow liver and spleen

4 The existence of hemodilution in patients with rheumatoid arthritis has been studied with dye and isotope dilution techniques (8 24 32 38). The total hemoglobin and blood volume were determined and the plasma and red cell volumes were calculated in patients with rheumatoid arthritis patients with iron deficiency anemia and in controls using the alveolar carbon monoxide method which does not appear to have been applied before in a study including patients

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CHAPTER I

HEMATOLOGICAL DATA AND CLINICAL ACTIVITY OF THE RHEUMATOID DISEASE

L. Engstedt & O. Strandberg

The anemia of rheumatoid arthritis has been studied for many years and by several workers but its pathogenesis is still in many ways obscure. In active stages anemia is a regular finding. Nilsson (22), reviewing earlier incidence studies, found anemia in his large material in 63 per cent of the women and 42 per cent of the men. Almost identical percentages were reported by Alexander & Duthie (2).

This anemia has been described as slightly hypochromic, normocytic and hyposideremic. The reticulocytes are slightly elevated (22), a slight hemolysis is reported by Freireich & al. (13) and Lewis & Porter (20). Biechl & al. (6) consider hemolysis to be a relatively unimportant factor in the mechanism of the anemia of rheumatoid arthritis. Mc Crea (8) regards an increased rate of red cell destruction as a factor in the production of anemia in some cases of active disease.

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Material and methods

Material

Patients. Three hundred consecutive in-patients from the department of rheumatology, Karolinska sjukhuset, Stockholm, 1958—1961, were chosen for frequency studies concerning hematological data. The patients, 183 women and 117 men, all with definite rheumatoid arthritis according to the A.R.A. criteria (3, 4), were investigated on admission before hospital therapy had started. From the women 101 patients were chosen at random and their previous and current therapy was tabulated (Table I). A protein study (Chapter V) was made on these 101 patients, who were chosen from the 183 female patients because their hematological and serum protein tests had been performed on blood drawn the same day. Their therapy can be considered as representative for the whole material. The figures for previous salicylate medication are certainly too low, because this medication was not routinely noted on admission. The

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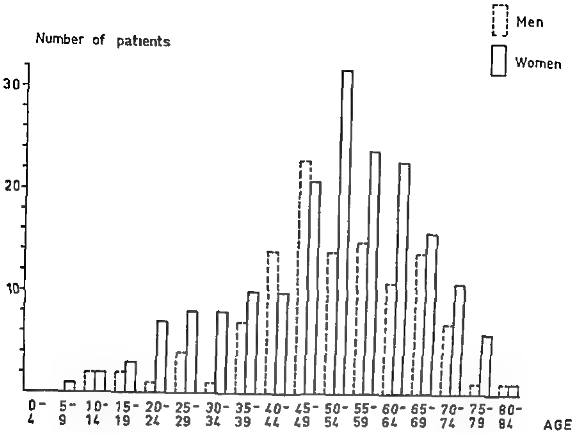


Fig 1
Age distribution of 300 patients with rheumatoid arthritis
183 women mean 51 3 years SD 15 years   117 men mean 51 6 years SD 14 years

other drugs are always checked up on a questionnaire

We excluded patients with additional diagnoses influencing the hematological system, such as bleedings from the gastro intestinal or urogenital systems and patients with clinically and serologically verified or suspected coexisting systemic lupus erythematosus Fig 1 shows the age distribution (*women mean* 51 3, SD 15 years, *men* mean 51 6, SD 14 years)

Controls Twenty subjectively healthy women, hospital staff or housewifes, without abnormalities in peripheral blood picture E S R and sternal marrow cytology Mean age 39 4 SD 16 years There was no history of previous blood donations Ten men with the same criteria as above Mean age 35 0, SD 10 years Hemoglobin concentration was determined in a group of 111 healthy conscripts 18 years of age

Laboratory methods

The blood samples were drawn in the morning when the patients were still in bed before the first meal The controls were examined immediately after arrival in the morning in the laboratory

a Hemoglobin concentration was determined in capillary blood as alkaline oxy

Table I

Therapy in 104 women with rheumatoid arthritis previous and present (on admission, i.e. immediately before the patients were studied)

Therapy	Previous	Present
	%	%
Gold	40.4	0
Corticosteroids	53.8	18.3
Salicylates	37.5	31.6
Iron tablets	14.4	6.7
Iron injection	3.8	0
Blood transfusion	7.7	0
Phenylbutazone	41.2	17.5
Chloroquine	29.8	17.3

hemoglobin in a Unicam spectrophotometer at 540 mm. Standardization with determination of the oxygen capacity of the blood was done at regular intervals using the van Slyke technique.

b. The number of red blood corpuscles was counted in capillary blood in a Burker chamber. Hayem's solution was used.

c. Serum iron concentration. Duplicate determinations with the orthophenanthroline method according to Agner (1) is routine in the department of clinical chemistry at the hospital, where these analyses were performed.

d. Erythrocyte sedimentation rate. The Westergren method (1 hour value) was used. No correction was made for anemia.

The errors of laboratory methods are given in Table II.

e. Statistical methods. Generally accepted methods were used for the statistical treatment with the calculation of the mean values and standard deviations. Student's t test for small samples was used to determine the level of significance (27).

The following significance levels were used:

*	0.05>P>0.01	Probably significant
**	0.01>P>0.001	Significant
***	P<0.001	Highly significant

Table II

Errors of laboratory methods, calculated from duplicate determinations

Laboratory method	Number of duplicate determinations	Range	Mean	Error of method $\pm\sqrt{\frac{\Sigma d^2}{2n}}$	Variation coefficient %
Hemoglobin, g/100 ml	0	[illegible] — 13.8	13.09	0.344	2.62
Red blood corpuscles, 10^6/mm³	10	3.33 — 4.7[illegible]	4.1[illegible]	0.134	3.[illegible]5
Serum iron, µg/100 ml	40	[illegible] — 19[illegible]	[illegible]6.1	4.94	6.50

Hemoglobin concentration, red cell count: from two different finger punctures, different pipettes. Serum iron concentration: determinations on the same sample on two subsequent days; the second sample had a code number.

Table III

Means and differences women—men with rheumatoid arthritis Comparisons between groups with E S R $\geq$ 50 and $<$ 50 mm/hour Hemoglobin concentration red cell count serum iron concentration and mean corpuscular hemoglobin The differences between the means are made on unabridged figures The significance of the differences between the means of the male and female patients is indicated

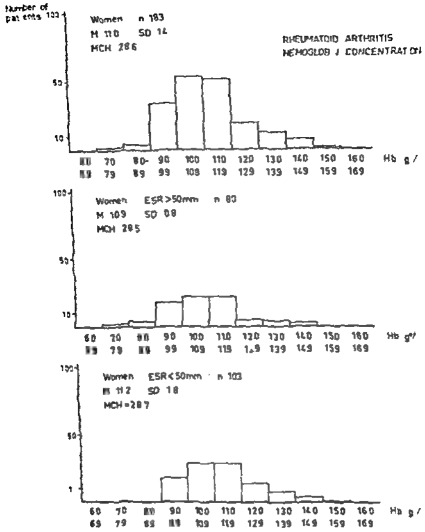
		n	Mean	Standard deviation	Difference between means
Hemoglobin conc women		183	11 0	1 43	1 0***
Hemoglobin conc men		117	12 1	1 87	
R B C women		183	3 96	0 46	0 28***
R B C men		115	4 13	0 52	
M C H women		183	28 6	1 81	0 48*
M C H men		115	29 1	1 96	
Serum iron women		160	66 9	34 0	0 51
Serum iron men		84	66 4	38 7	
Hb conc women	ESR $\geq$ 50 mm	80	10 9	0 81	0 28
Hb conc women	ESR $<$ 50 mm	103	11 2	1 76	
Hb conc men	ESR $\geq$ 50 mm	53	11 7	1 92	0 69*
Hb conc men	ESR $<$ 50 mm	64	12 4	1 78	
R B C women	ESR $\geq$ 50 mm	80	3 77	0 52	0 15*
R B C women	ESR $<$ 50 mm	103	3 92	0 40	
R B C men	ESR $\geq$ 50 mm	52	4 01	0 56	0 23*
R B C men	ESR $<$ 50 mm	63	4 24	0 45	
M C H women	ESR $\geq$ 50 mm	80	28 5	2 01	0 19
M C H women	ESR $<$ 50 mm	103	28 7	1 60	
M C H men	ESR $\geq$ 50 mm	52	29 3	1 76	0 31
M C H men	ESR $<$ 50 mm	63	29 0	2 12	
Serum iron women	ESR $\geq$ 50 mm	68	56 1	28 4	18 8***
Serum iron women	ESR $<$ 50 mm	92	74 9	35 8	
Serum iron men	ESR $\geq$ 50 mm	39	50 2	27 3	30 2***
Serum iron men	ESR $<$ 50 mm	45	80 4	41 9	

Results

The hemoglobin concentration mean corpuscular hemoglobin (M C H) and serum iron values of the patients are recorded in figs 2 5 and Table III The patients show a moderate anemia with no difference in M C H (in the men), or a very slight drop (in women) compared to the normal material

The hemoglobin concentration and the number of red cells are slightly but significantly lower in women than in men The difference in M C H is very small and the *serum iron* values are identical

A comparison between patients with E S R $<$ 50 mm/h and patients with $\geq$ 50 mm h shows significant differences in serum iron concentration in both women and men Hemoglobin concentration red cell count and M C H show no significant differences The



Fig

Distribution of hemoglobin values in 183 women with rheumatoid arthritis

group with E S R ≥ 50 mm/h can be considered to have a higher disease activity than the patients with E S R < 50 mm/h, according to Nilsson (22) Shetlar & al (25) and Bottiger Malmquist & Olhagen (7)

Grouping 104 of our female patients according to clinical activity (25) *confirms* this see Table VI

The correlations between E S R serum iron and hemoglobin concentration have

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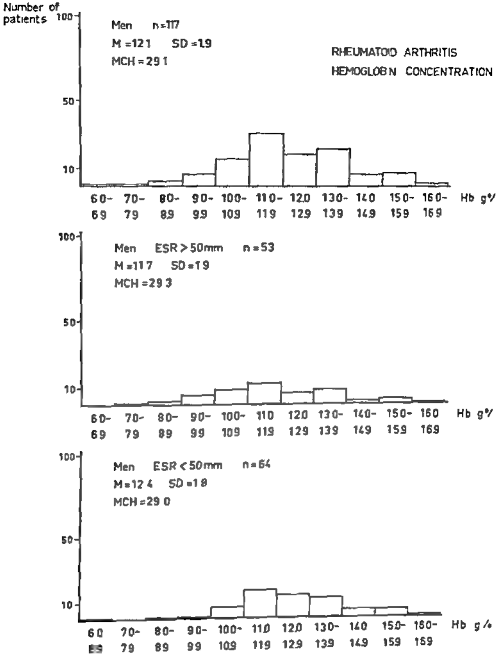

Fig 3
Distribution of hemoglobin values in 117 men with rheumatoid arthritis

been studied in 104 women and 44 men All correlations are significant except between E S R and serum iron concentration in the women (Table IV) Partial correlation analysis (Table V) gives different results for women and men The correlation coefficient between E S R and hemoglobin concentration, with elimination of serum iron (Table V) is significant in women but not in men Comparing E S R and serum iron

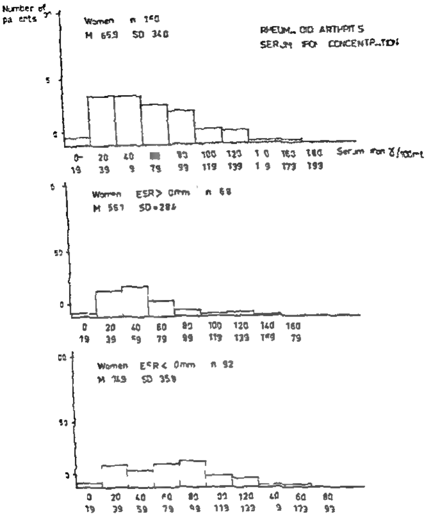

Fig. 4
Distribution of serum iron values in 160 women with rheumatoid arthritis

with Hb eliminated does not change the significance. The correlation coefficient between serum iron and hemoglobin after elimination of E.S.R. does not change the significance in men, but diminishes the significance from the 1 per cent level to insignificant in women. However, it is difficult to draw far reaching conclusions from partial correlation analysis, as is pointed out by Fisher (12). As Table V shows there

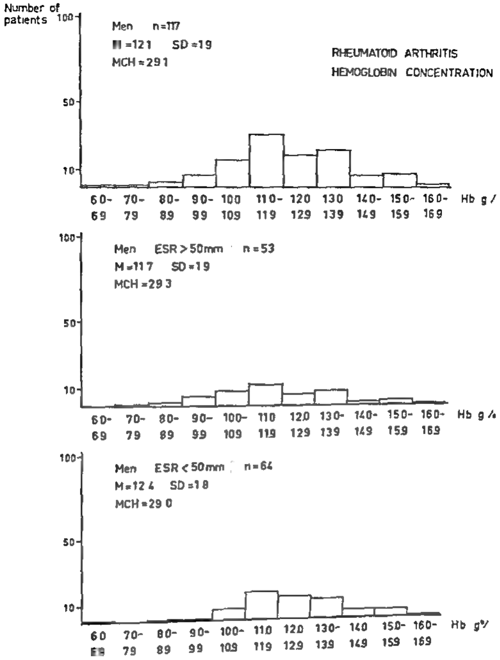

Fig 3
Distribution of hemoglobin values in 117 men with rheumatoid arthritis

been studied in 104 women and 44 men All correlations are significant except between E S R and serum iron concentration in the women (Table IV) Partial correlation analysis (Table V) gives different results for women and men The correlation coefficient between E S R and hemoglobin concentration, with elimination of serum iron (Table V) is significant in women but not in men Comparing E S R and serum iron

Table IV

Relations between hemoglobin concentration serum iron concentration and erythrocyte sedimentation rate in 104 women and 43 men with rheumatoid arthritis

Variables	Women				Men			
	n	Mean	S D	r	n	Mean	S D	r
E S R mm/1 hour	104	47 1	27 8	—0 20**	43	49 0	28 8	—0 41**
Hemoglobin g/100 ml	104	10 4	1 1		43	11 4	1 6	
E S R mm/1 hour	104	47 1	27 8	—0 14	41	49 2	28 8	—0 69***
Serum iron µg/100 ml	104	70	35		41	74	43	
Serum iron µg/100 ml	104	70	35	0 20**	42	73	43	0 59**
Hemoglobin g/100 ml	104	10 4	1 1		42	11 2	1 6	

none group II mild group III moderate group IV severe activity A complete statistical account of the differences between the means for the hematological data of the clinical activity groups has been made but is not reported here In Table VI groups I and II representing low clinical activity are together compared with the combined groups III and IV with higher clinical activity Highly significant differences were found for the means of hemoglobin serum iron and E S R between the low and the high activity groups The means for the red blood cell count are significantly different at the 1 per cent level in the same comparison The M C H means of low and high activity groups are not statistically different Thus M C H does not vary either with clinical activity or with E S R (Table III) in this patient material

Table V

104 women and 44 men with rheumatoid arthritis Partial correlations between the variables E S R, hemoglobin and serum iron concentrations

	104 women	44 men
E S R Hb	—0 289***	—0 414**
E S R Hb serum iron	—0 263**	—0 017
E S R serum iron	—0 137	—0 689***
E S R serum iron Hb	—0 058	—0 604***
Serum iron Hb	0 290**	0 587***
Serum iron Hb E S R	0 180	0 457***

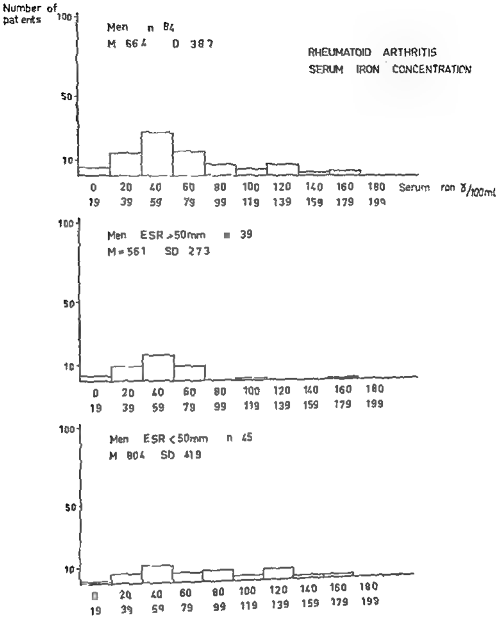

Fig 5
Distribution of serum iron values in 84 men with rheumatoid arthritis

were not the same tendencies in men and women in the partial correlations possibly because the variables are influenced by different factors in women and men e g hormonal influences (17 18 29)

The means of *Hb* concentration serum iron concentration and E S R in groups with different clinical activities are compared in Table VI Clinical activity is classed according to *Shetlar & al* (25) group I slight or

Table VIII

Red blood cell count in patients with rheumatoid arthritis and adult healthy persons
Means reported by earlier and present authors

Author	Women				Men			
	n	Mean	± εM	SD	n	Mean	± εM	SD
Healthy persons								
Wahlquist (29)	49	4 41	0 05	0 32	50	5 01	0 05	0 36
Nilsson (Umeå, 27)	66	4 474	0 039	0 314	68	4.844	0 038	0 313
Nilsson (Uppsala 22)	64	4 344	0 053	0 43	58	5 260	0 056	0 42
Totterman (28)	66	4 41	0 07	0 19	67	4 86	0 03	0 21
Whitby & Britton (32)		4 80	(4 3-)			5 50	(4 5)	
Wintrobe (33)		4 8		0 6*)		5 4		0 8*)
Present authors	20	4 16	0 04	0 70	10	4 58	0 11	0 35
Rheumatoid arthritis patients								
Nilsson (Umeå, 27)	207	4 345	0 024	0 338	130	4 708	0 041	0 465
Nilsson (Uppsala 22)	56	4 197	0 062	0 463	41	4 524	0 064	0 408
Jeffrey (15)	66	4 11	0 05-	0 42	34	4 45	0 079	0 46
Richmond & al (23)	38	4 94		0 56	26	4 94		0 37
Freireich & al (13)	20	4 32	0 076	0 34	17	4 48	0 15	0 51
Present authors	183	3 86	0 034	0 46	115	4 13	0 048	0 52

*) Limits for 93 per cent of the values

Discussion

Comparison with other materials

Before interpreting these results it seems worth comparing them with previous investigations

a Hemoglobin concentration (Table VII)

Controls Our results do not deviate essentially from other Scandinavian normal materials (11 22 28 30) They are lower than the averages of Whitby & Britton (32) and Wintrobe (33) the normal figures of the last mentioned text book are a compilation of data up to 1933

Rheumatoid arthritis patients The mean for our 183 women (11 0 g/100 ml) is about the mean of figures published earlier The mean for the 117 men (12 1 g/100 ml) is lower than in earlier materials with a rather large range and standard deviation The means for the rheumatoid arthritis patients are significantly lower than those for the control group as in previous materials

b Red blood cells (Table VIII)

Controls Our values are not very different from Scandinavian figures but rather low compared with the text books mentioned

Table VI

Differences between means for concentrations of hemoglobin and serum iron E S R, red cell count and mean corpuscular hemoglobin in 104 women with rheumatoid arthritis Comparisons between low clinical activity (Shetlar groups I and II) and high (groups III and IV cf ref 25)

Variable	Activity group	n	Mean	Difference	P
Hemoglobin concentration	I + II	38	11.0	1.0	<0.001
	III + IV	66	10.1		
Serum iron concentration	I + II	38	85	23	<0.001
	III + IV	66	62		
E S R	I + II	38	34.0	19.2	<0.001
	III + IV	66	53.2		
R B C	I + II	38	3.84	0.26	0.01>P>0.001
	III + IV	66	3.58		
M C H	I + II	38	28.1	0.57	<0.05
	III + IV	66	28.2		

Table VII

Hemoglobin concentration in patients with rheumatoid arthritis and adult healthy persons Means reported by earlier and present authors

Author	Women				Men			
	n	Mean	± εM	SD	n	Mean	± εM	SD
Healthy persons								
Vahlquist (29)	50	13.48	0.12	0.87	50	15.68	0.1[illegible]	0.86
Nilsson (Umeå 22)	66	12.68	0.10	0.82	68	13.98	0.12	0.93
Nilsson (Uppsala 22)	64	13.62	0.13	1.03	58	15.93	0.11	0.84
Totterman (28)	66	12.05	0.06	0.52	67	13.73	0.08	0.68
Whitby & Britton (32)		13.7	(12–15.5)			15.6	(14–17)	
Wintrobe (33)		14.0		2.0*)		16.0		2.0*)
Present authors	20	12.2	0.14	0.60	111	15.4	0.07	0.69
Rheumatoid arthritis patients								
Nilsson (Umeå 22)	207	11.51	0.09	1.03	130	13.26	0.11	0.84
Nilsson (Uppsala 22)	56	11.9	0.21	1.56	41	13.2	0.23	1.47
Jeffrey (15)	120	10.7		1.35	80	12.6		1.40
Richmond & al (23)	38	10.9		0.9	26	12.4		1.2
Freireich & al (13)	20	11.28	0.23	1.05	12	12.28	0.57	1.97
Present authors	183	11.0	0.11	1.43	117	12.1	0.17	1.87

*) Limits for 93 per cent of the values

Table X

Serum iron concentration in patients with rheumatoid arthritis and healthy adult persons
Means reported by earlier and present authors

Author	Women				Men			
	n	Mean	± εM	SD	n	Mean	± εM	SD
Healthy persons								
Skouge (26)	50	104.4	3.0	21.6	50	117.7	2.8	19.7
Vahlquist (29)	50	123.0	4.5	31.6	50	142.0	6.1	43.0
Vahlquist & Neander (30)	40	114.0	5.9	37.2	36	11[illegible].7	3.7	22.0
Høyer (14)	50	114.8	4.3	30.6	50	131.2	4.2	30.0
Lovgren (21)	40	105.0	6.0	37.9	17	135.0	7.5	30.9
Waldenstrom (31)	15	113.2	8.2	31.8				
Laurell (19)	39	108			61	124		
Nilsson (22)	21	103.8	7.0	35.9	26	13[illegible].0	3.9	17.7
Rustung (24)	24	101.9	5.5	27.0	19	119.6	6.7	29.3
Tötterman (28)	67	121.5	3.5	28.5	66	140.0	4.[illegible]	34.7
Andersson (5)	50	105.4	4.6	32.6	20	115.4	5.7	25.6
Present authors	19	101.1	9.1	39.7	8	117.5	19.1	54.1
Rheumatoid arthritis patients								
Nilsson (Umea, 22)	129	74.7	2.9	33.4	80	96.1	4.8	42.[illegible]
Jeffrey & al (15)	1[illegible]0	55	2.8	31	80	71	3.8	34
Richmond & al (23)	35	80		29	23	9[illegible]		11
Ebaugh (12)	16	48.3		25	6	[illegible]2.7		37
Present authors	160	66.9	2.[illegible]	34.0	84	66.4	4.2	38.7

authors cited have higher values for men and Nilsson (22) has a significant difference between women and men. Our patients have a highly significantly lower serum iron concentration than the controls. The difference between controls and patients is of the same order as in the material of Nilsson (about 30 μg/100 ml).

Iron metabolism and the type and degree of anemia

In active rheumatoid arthritis there is always a marked hyposideremia. Yet the bone marrow — unless there is not a true sideropenia — generally contains demonstrable iron stores. Mc Crea (8)) found 11 out of 33 patients with rheumatoid arthritis without marrow iron histologically and in 10 of these 11 patients the hemoglobin level rose by > 2 g per 100 ml after intravenous iron therapy: they thus had iron deficiency. Richmond & al (23) reported similar findings: in 31 per cent of 64 patients the bone marrow was iron negative with the potassium ferrocyanide method but chemically determined all of 32 patients had marrow iron

Table IX

Mean corpuscular hemoglobin in patients with rheumatoid arthritis and healthy adult persons. Means reported by earlier and present authors

Author	Women				Men			
	n	Mean	$\pm \varepsilon M$	S D	n	Mean	$\pm \varepsilon M$	S D
Healthy persons								
Vahlquist (29)	49	30.7	0.3	2.0	50	31.4	0.3	2.5
Nilsson (Uppsala 22)	64	31.54	0.38	3.01	57	30.43	0.28	2.12
Whitby & Britton (32)		29.6	(27—32)			29.6	(27—32)	
Wintrobe (33)		29		2*)		29		2*)
Present authors	20	29.4	0.16	0.72	10	29.4	0.22	0.69
Rheumatoid arthritis patients								
Nilsson (Uppsala 22)	56	28.89	0.46	3.46	41	29.38	0.41	2.62
Jeffrey (15)	66	24.8	(14.6—31.6)		34	25.5	(18.6—33.3)	
Freireich & al (13)	20	26.2	0.57	2.57	12	27.3	0.93	2.87
Present authors	163	28.6	0.13	1.81	115	29.1	0.18	1.96

*) Limits for 93 per cent of the values

Rheumatoid arthritis patients. Our patients had lower figures than those for materials published earlier. Like Nilsson (22) we found no significant difference between healthy and arthritic men.

c. Mean corpuscular hemoglobin (Table IX)

Controls. There are no differences between our figures and those for previous materials.

Rheumatoid arthritis patients. Our figures are very similar to those of Nilsson (22). The differences between the means for the controls and the patients are not significant. Nilsson had a significant difference between healthy and rheumatoid females but not between male controls and patients. Freireich & al (13) had a lower mean (female + male) for arthritic patients than for controls. Jeffrey (15) had rather low means for patients with rheumatoid arthritis suggesting a high frequency of sideropenic patients (rather high T.I.B.C. values).

d. Serum iron concentration (Table X)

Controls. The means for our own controls do not differ from the cited materials. All published means have standard deviations between 22 and 43 $\mu g/100$ ml (see Totterman 28). As the blood for analysis was always drawn at the same time in the morning the diurnal variation (Vahlquist 29) can be ignored.

Rheumatoid arthritis patients. The present values do not differ from those published earlier. There is no difference between the means for our female and male patients. The

Table X

Serum iron concentration in patients with rheumatoid arthritis and healthy adult persons. Means reported by earlier and present authors

Author	Women				Men			
	n	Mean	± εM	SD	n	Mean	± εM	SD
				Healthy persons				
Skouge (26)	50	104.4	3.0	21.6	50	117.7	7.8	19.7
Vahlquist (29)	50	123.0	4.5	31.6	50	147.0	6.1	43.0
Vahlquist & Neander (30)	40	114.0	5.9	37.7	36	117.7	3.7	0
Høyer (14)	50	114.8	4.3	30.6	50	131.7	4.2	30.0
Lövgren (21)	40	105.0	6.0	37.9	17	135.0	7.5	30.9
Waldenström (31)	15	113.7	8.2	31.8				
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Nilsson (22)	21	103.8	7.0	35.9	76	137.0	3.9	17.7
Rustung (24)	24	101.9	5.5	27.0	19	119.6	6.7	29.3
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Present authors	19	101.1	9.1	39.7	8	117.5	19.1	54.1
				Rheumatoid arthritis patients				
Nilsson (Lund, 22)	149	74.7	2.9	33.4	80	96.1	4.8	42.7
Jeffrey & al (15)	120	55	2.8	31	80	71	3.8	34
Richmond & al (23)	35	80		29	23	9		11
Ebaugh (12)	16	49.3		25	6	72.7		37
Present authors	160	66.9	2.7	34.0	84	66.4	4.2	38.7

authors cited have higher values for men and Nilsson (22) has a significant difference between women and men. Our patients have a highly significantly lower serum iron concentration than the controls. The difference between controls and patients is of the same order as in the material of Nilsson (about 30 μg/100 ml).

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In 57 patients with rheumatoid arthritis, we found only 10 (18 per cent) without histochemically demonstrable bone marrow iron, and all had marrow iron chemically determined (Johansson & Strandberg, to be published). Thus true sideropenia with empty iron stores is infrequent in patients with uncomplicated rheumatoid arthritis. In the present material, patients with complicating diseases that are followed by sideropenia have been excluded (see patient material p. 2). The actual therapy was not considered to exert any influence on the relationship between clinical activity and hematological data.

The present material shows normal M.C.H. in men with rheumatoid arthritis and a very slight reduction in women. We have found a very slight reduction of the red cell hemoglobin concentration (M.C.H.C.) in another material (Chapter II). This agrees with the results of e.g. Nilsson (22). Other authors have found appreciably lower values for M.C.H., and to some extent also for M.C.H.C. (e.g. Jeffrey, 15). This is probably explained by the inclusion of patients with true sideropenia, as is also pointed out by Jeffrey. The presence of iron deficiency in his patient material is also indicated by the high transferrin values. In a smaller group of patients we have found lower transferrin values in the arthritis group than in the controls. This was first shown by Laurell (19). Nilsson (22) found lowered M.C.H. in patients with rheumatoid arthritis compared with the controls and a diminished diameter of the red blood corpuscles. He concluded that there is no real change in the size of red blood cells in these patients, but rather a change of shape and that the bone marrow retains its capacity to produce hemoglobin. Freireich & al. (15) found a lower average M.C.H., M.C.V. and M.C.H.C. in a group of rheumatoid arthritis patients, indicating that the patients had a slightly hypochromic anemia. In our patients with rheumatoid arthritis the red cells show only a very slight decrease of M.C.H. The degree of anemia, as measured by hemoglobin and serum iron, varies with the clinical activity, but M.C.H. does not decrease significantly with increasing clinical activity and E.S.R. (Table VI). We have found (Chapter II) that there seems to be a tendency for M.C.H. to decrease more in iron deficiency anemia than in rheumatoid arthritis anemia. In 5 men and 7 women with iron deficiency anemia and a mean hemoglobin concentration of 9.8 g/100 ml. M.C.H. was 25.7 micromicrogram (Chapter II). In the present material 66 women with rheumatoid arthritis in activity groups III and IV had a hemoglobin concentration of 10.1 g/100 ml and their M.C.H. was 28.2 micromicrogram. Nor is there any significant decrease of M.C.H. in the high activity group as compared with the low activity group even though the anemia is more pronounced in the former (Table VI). These observations may indicate that a faulty iron incorporation is not the main cause of the anemia in rheumatoid arthritis.

Summary

Three hundred in-patients (183 women and 117 men) with rheumatoid arthritis according to the A.R.A. criteria have been studied with respect to hemoglobin and serum iron concentrations, red cell count, mean corpuscular hemoglobin and E.S.R. Comparisons have been made with controls and materials published earlier.

One hundred and four of the females have been selected at random and analysed in respect of clinical activity and actual therapy correlations between their hematological values and clinical activity have been studied

Hemoglobin concentration and the red cell count are reduced in patients with rheumatoid arthritis but the mean M C H for both women and men lies within normal limits In active cases of rheumatoid arthritis there is a hypoferremia that is not a sign of a real sideropenia

Significant differences between women and men were found in hemoglobin concentration and red cell count but not in M C H and serum iron concentration

Comparisons between the mean hematological values with the patients grouped according to E S R $\geq$ 50 mm and $<$ 50 mm/hour showed significant differences only in serum iron

Statistically significant correlations were obtained between E S R versus hemoglobin and serum iron versus hemoglobin in both women and men and between E S R and serum iron in men but not in women

Comparisons between the mean hematological values and E S R with the material grouped according to disease activity measured with clinical parameters exclusively showed statistically highly significant differences between low and high activity groups in respect of hemoglobin serum iron and E S R Erythrocyte values were different at the 1 per cent level but M C H showed no significant differences between the activity groups Thus the anemia of rheumatoid arthritis as measured with Hb concentration red blood cell count and serum iron runs parallel to clinical activity but M C H is not significantly correlated to clinical activity or the level of E S R.

Acknowledgements

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CHAPTER II

THE ABSORPTION AND UTILIZATION OF IRON IN PATIENTS WITH RHEUMATOID ARTHRITIS, IRON DEFICIENCY AND IN CONTROLS

L Engstedt & O Strandberg

The literature concerning the iron metabolism in patients with rheumatoid arthritis has been excellently summarized up to 1962 by Alexander & Duthie (2) In spite of lowered serum iron and anemia with signs of hypochromia with slightly decreased M C H and M C H C (44, 20), the anemia is refractory against orally administered iron (11, 13, 51, 52, 49, 28, 29, 31)

Parenteral iron therapy with the administration of large doses of saccharated oxide of iron is said to give an initial response in hemoglobin values in some patients but seldom continued improvement (51 52, 49 28, 29, 30 42, 43)

Jeffrey & al (31) have classified the anemia in rheumatoid arthritis into two main types (1) a hypochromic and sometimes microcytic anemia with reduced marrow iron stores which responds well to parenteral iron therapy, (2) a normochromic anemia with reduced cell count, similar to the anemia of infection and refractory to all therapy The iron deficiency type was much the more common among their patients The absorption of radioiron from the gastrointestinal tract was generally considerably greater in the rheumatoid subjects than in the controls

When we studied the frequency and type of anemia in our patients with rheumatoid arthritis (60) hypochromia was found less frequently than in the material of Jeffrey & al (31) Preliminary results (19) showed that the absorption and utilization of radioiron were decreased in our patients with rheumatoid arthritis, compared with the controls

This paper concerns the absorption and utilization of inert and labelled iron in patients with rheumatoid arthritis and true sideropenia as well as in controls The results indicate a decreased iron absorption in arthritic subjects

MATERIAL AND METHODS

Material

a Patients with rheumatoid arthritis

The thirty two cases studied were in patients at the department of rheumatology with classical and definite active rheumatoid arthritis according to the diagnostic criteria of the American Rheumatism Association (A R A 3 4 5) and with clinical activity II—IV according to Shetlar & al (50) The patients were also classified with respect to rheumatoid progression and functional capacity according to Steinbrocker & al (56) Relevant clinical data including previous therapy with chrysotherapy corticosteroids phenylbutazone blood transfusions and iron therapy are summarized in Table I The previous therapy was considered too

Table 1

DIAGNOSTIC DATA 27 WOMEN WITH RHEUMATOID ARTHRITIS

No	Subject	Age	Duration of the disease years	Titer of rheumatoid factor	Clinical classification Steinbrocker & al (36): Rheumatoid progression stage	Clinical classification Steinbrocker & al (36): *Functional* capacity class	Clinical activity Shetlar & al (30)	Previous therapy[1]: Bt	Au	Fe	St	Pb	Cq
1	AB	48	8	1 512	IV	III—IV	IV		+		+		
2	OL	37	10	1 1024	II	II	III		+			+	
3	SS	48	14	Neg	III	III	II		+	+	+		
4	VK	53	1	1 1024	III	III	III						
5	KA	46	4	1 64	II	II	II			+	+		
[illegible]	EE	53	13	1 2048	II	II	II		+				
7	SS	56	20	1 512	IV	IV	II	+					
8	AC	55	0	1 8192	III—IV	III—IV	II						
9	HS	51	23	1 32768	III	III	IV	+		+			
10	MA	47	½	1 4096	II	III	IV				+		
11	KS	57	6	1 1024	III	III	III		+	+			
1	MF	58	½	1 56	II	II	IV						
13	KJ	63	5	1 512	II	II	IV			+			+
14	EG	7	¾	1 256	II	II	IV			+			+
15	EC	70	34	1 2048	III	III	III	+		+			
16	GA	25	10	1 512	II	II	II		+	+	+	+	
17	BJ	9	10	1 2048	II	II	III		+		+	+	
18	EM	69	33	1 256	III—IV	IV	III				+	+	
19	AN	54	1	1 1 8	II	II	II						
[illegible]	DD	61	5	1 128	II	III	III						
1	RW	57	2	1 1024	II	II	II				+	+	+
2	EH	60	5	1 512	III	II—III	III			+			
3	EH	54	20	1 2048	III IV	III—IV	II		+		+	+	
24	HR	57	5	1 1024	III	III—IV	III				+	+	
25	SP	67	15	1 56	II	III	II			+		+	
6	KE	55	1½	Neg	I—II	II	III						
27	AS	55	6	1 4096	II	II	II						

Therapy with
Bt — Blood transfusion
Au — Gold
Fe Iron
St — Corticosteroids
Pb = Phenylbutazone
Cq Chloroquine

distant in time to exert any influence on the present study (i e more than one year be fore the examination) Two patients with recent hematinic therapy were an excep tion, and have been discussed separately The therapy during the test period consisted of vitamins, salicylates and physiotherapy Mean age women 50 1 years, range 15—70, men 36 0 range 22—48

Patients having signs of other diseases or complications affecting the hematological system were excluded as were patients with arthritis of non rheumatoid origin, according to A R A (3, 4, 5) Thus 8 patients were excluded for the following reasons repeated prolonged menstrual bleedings, positive LE cell tests combined with highly elevated gam ma globulin in serum, bilateral renal tuber culosis with hematuria iron deficiency prob ably originating from earlier resection of the stomach (58, 45)

Two female patients (No 3 and 26 Table I) had negative rheumatoid factor tests, but adequately met the criteria for the diag nosis rheumatoid arthritis

Another eighty three patients, 59 women and 24 men with rheumatoid arthritis ac cording to the criteria mentioned above were studied with respect to the serum iron elevation after an oral iron tolerance test (62)

b Patients with iron deficiency

Seven women and five men with clinical signs (69) and laboratory findings charac teristic of iron deficiency comprised this group Mean age women 38 7, range 23—50, men 45 0 range 30—67 Sections of the bone marrow, aspirated from the sternum and stained with potassium ferrocyanide did not reveal hemosiderin in any of these patients (46 64) From this group had been rejected two women with cancer in the upper digestive tract and four wo- men and four men with iron deficiency due to various malabsorptive states in the gastro intestinal tract, forming a he terogeneous group which is of course unsuitable for iron absorption studies of the present type One of the subjects included in this group was an example of latent iron deficiency (7) he had donated 107 bottles of blood (400 ml each) during the 5 years preceeding the test, and had nor mal blood values but empty iron stores, he had no clinical signs of iron deficiency

c Controls

Twenty one women (hospital staff and housewives) and 7 men, all subjectively healthy and working full time, with normal blood picture, E S R and paper electrophore tic pattern, in twenty (15 women and 5 men) the bone marrow was examined and showed normal morphology and normal histochemical iron content Mean age wo men 40 0 range 17—69 men 37 7 range 23—71

Laboratory methods

a Erythrocyte sedimentation rate The Westergren method (1 hour value) was used No correction was made for anemia

b Hemoglobin concentration was deter mined in venous blood as alkaline oxyhemo globin in a Bausch & Lomb spectrophoto meter at 540 nm

Standardizations with determination of the oxygen capacity of the blood was done at regular intervals using the van Slyke technique

Duplicate determinations were used in all cases from the same blood sample Determi

nation of hemoglobin concentration red blood cells and packed cell volume was made in all cases 2 or 3 times a week during the test period (14—21 days)

c Red blood corpuscles were counted in a Burker chamber All analyses were performed by the same person (venous blood)

d Reticulocytes were counted according to Larsson & Svensson (35) One thousand cells were counted

e The volume of packed red cells was determined with an International hematocrit centrifuge type M B (International Equipment Boston Mass USA) which has a speed of 11 500 r p m Venous blood from heparinized tubes was centrifuged 5 or 10 minutes duplicate determinations were made

Correction for trapped plasma (9) was made with 1 7 per cent when the samples were centrifuged 5 minutes and 1 3 per cent when they were centrifuged 10 minutes according to Garby & Vuille (21)

f Serum iron concentration Double determinations with the orthophenantroline method (1) were made at the department *of clinical chemistry at the hospital*

g Iron absorption after the administration of 0 5 g ferrosi lactas tablets according to Waldenstrom (62) was determined for each subject More than 200 such iron loadings in which the serum iron concentration has been studied for up to 6 hours have shown that as a rule the serum iron curve reaches its maximum about two hours after administration of the iron (see also Waldenstrom 62) Consequently the test has been simplified to only two analyses one before the test and the other two hours after administration of the iron tablet This test was always done in the morning with the subject fasting overnight.

h Transferrin Serum samples were kindly analysed at Laurell s laboratory in Malmö method according to Laurell (36)

i Endogenous COHb production was determined at the department of clinical physiology using the alveolar carbon monoxide method of Sjostrand (53) with modifications (39 40 70) Double determinations were made except in 2 controls and 3 patients with rheumatoid arthritis in whom only one determination was made Only values from non smokers were registered (see 18 53)

k The total hemoglobin was determined *by the alveolar CO method of Sjöstrand* (54) Duplicate determinations were made except in the cases mentioned above

l Iron absorption with labelled iron was estimated as follows 6—12 μC Fe^{59} in ferric chloride with high specific activity (2—25 μC per mg Fe) in hydrochloric acid solution (Philips Holland Abbott Oak Ridge USA) was mixed in a drinking glass containing 50 ml aqua dest 0 5 ml concentrated hydrochloric acid, and 89 mg *ferrous chloride = 25 mg* Fe^{++} *as carrier* The test dose was left overnight at room temperature The solution was given to the subjects at 8 a m after they had fasted overnight The glass was rinsed three times and the test subject drank the rinse water No significant radioactivity then remained in the drinking glass The subjects were not allowed to eat or drink for 3 hours after the test dose After the administration of Fe^{59} feces were collected quantitatively by well trained staff for 6—11 days In one case collection continued for 18 days The fecal collection was terminated when a single day s specimen contained <0 5 per cent of the Fe^{59} dose administered

3

Blood samples were drawn 2 or 3 times a week for 14—21 days

Urine was collected in a few cases for a week after the test dose had been given As the samples always contained negligible amounts of radioactivity, urine losses were disregarded (see Jeffrey & al 31)

Measurement of radioactivity in the samples (i) Feces The feces collected during 24 hours were homogenized with water, carrier iron and a detergent (Tend), using a high speed blender (24,000 r p m Ultra Turrax) The mixture was weighed and triple aliquots of 5 ml were pipetted into plastic tubes that fitted the well of the gamma scintillation crystal The small aliquots were weighed

(ii) Blood The blood samples were hemolysed with saponinum purum Two aliquots of 5 ml were measured for radioactivity in the same way as the feces samples

(iii) Standards An aliquot of the original radioactive solution was used as standard It was pipetted with an Agla micrometer syringe diluted with aqua dest, and ferrous sulphate was added as a carrier The solution was acidified with hydrochloric acid to prevent precipitation of the iron and subsequent adherence to the glass

Radioactivity was measured on 5 ml samples of hemolyzed whole blood and feces in a scintillation detector with a well crystal (Tracerlab P 20 B W, connected to a Tracerlab Superscaler S C — 18 A) A fully automatic sample changer was used The counting efficiency for Fe^{59} with this equipment was 20 per cent Ten thousand impulses were counted for every sample and as triple fecal and double blood aliquots from every sample from the subjects were measured, the accuracy was well within ± 2 per cent (63) The amount of radioactivity in the blood and fecal specimens was calculated by comparison with simultaneously measured 5 ml triple aliquots of the standard solution

In a comparison of total errors of measuring iron absorption with the fecal recovery method and with total body monitoring the error with the former method has been estimated to be about 10 per cent and is greater than the error for total body monitoring (38) These authors found a correlation coefficient between the two methods of >0 8 and pointed to the risk of incidental errors because of incomplete feces collection this error will result in excessively high absorption values In the present investigation, all persons suspected of having cooperated badly in this respect have been excluded or the test was repeated

The absorption of Fe^{59} is here considered to be the retained dose of Fe^{59} i e the dose administered less the value of fecal recovery (compare Garby & Sjolin, 22)

The erythrocyte utilization of absorbed iron was estimated from the radioactivity found in the blood samples 14—21 days after the administration of the test dose and the blood volume determinations with the carbon monoxide method (53) during the test period

m Histamine test The subject fasted over night The acidity of three 20 minute periods was determined after administration of 0 5 mg histamine subcutaneously

In a few cases the gastric acidity was determined with the Diagnex test

n Bone marrow iron examinations were made with the potassium ferrocyanide technique on marrow sections using the method of Rath & Finch (46), slightly modified by Stenninger & Brante (57)

Table II

ERRORS OF LABORATORY METHODS CALCULATED FROM DUPLICATE DETERMINATIONS

Values from consecutive subjects

Laboratory method	Number of duplicate determinations	Range	Mean	Method error $\pm\sqrt{\frac{\sum d^2}{2n}}$	Variation coefficient % of mean
Hemoglobin g/100 ml	21	9 3 — 14 3	11 96	0 195	1 64
Red blood corpuscles 10^6/mm³	10	3 53— 4 72	4 12	0 134	3 25
Serum iron µg/100 ml	40	76 —196	76 1	4 94	6 50
Reticulocytes per cent	21	0 65— 2 40	1 51	0 556	36 7
Packed cell volume per cent	1	31 0 — 47 8	38 17	1 76	4 61
COHb saturation per cent	28	0 26— 1 14	0 56	0 1	21 5
Total hemoglobin,	28	311 —655	464	18 7	4 0

Hb concentration packed cell volume samples from two different venipunctures at 1—2 days interval
Red blood corpuscles from two different finger punctures different pipettes
Reticulocytes different slides from same finger puncture
Serum iron determinations on two subsequent days the second sample had a code number
COHb and total Hb determinations on two consecutive days

o Other methods applied All subjects were examined with Coombs test basal metabolic rate x ray examination of the abdomen with respect to enlarged liver and spleen (except in a few controls) Leucocyte and thrombocyte counts were normal in all subjects The haptoglobin concentration in the serum was also determined in a part of the material

The rheumatoid factor test was made by the method of Svartz Schlossman (61) at Professor Svartz s laboratory

p Statistical methods The statistical treatment was done by generally accepted methods with calculation of mean values and standard deviations (55) The errors of some of the methods are summarized in Table II

Because there were so few subjects in the male and sideropenic groups statistical calculations of significance have been made only for the differences between healthy and rheumatoid women (see Table III)

Results

a Hematological values

The patients with rheumatoid arthritis have a real anemia with a decrease of the hemoglobin concentration as well as the total hemoglobin amount (Table III 2 16—19)

M C H and M C H C (mean corpuscular hemoglobin mean corpuscular hemoglobin concentration) are decreased in the rheuma

Table III

RESULTS OF HEMATOLOGICAL AND OTHER INVESTIGATIONS IN PATIENTS AND CONTROLS

The statistical significance of the differences between the means for the groups of women with rheumatoid arthritis and the control women is indicated

	n	M	S D	Range
1 E S R mm/1 hour				
Rheum arthr women	27	59 3***	29 3	6—123
Rheum arthr men	5	58 4	35 1	39—121
Iron deficiency women	7	20 1	14 5	5—37
Iron deficiency men	5	14 0	13 3	3—33
Controls women	21	9 3	6 0	1—20
Controls men	6	5 5	6 0	2—17
2 Hemoglobin conc g/100 ml				
Rheum arthr women	27	10 66***	0 87	8 4—12 2
Rheum arthr men	5	11 48	1 53	9 7—13 1
Iron deficiency women	7	8 91	2 08	7 8—11 9
Iron deficiency men	5	11 12	2 29	8 8—14 5
Controls women	21	12 92	0 63	11 4—14 7
Controls men	7	13 46	1 01	11 1—14 7
3 Red blood cells 10^6				
Rheum arthr women	27	3 69***	0 25	3 2—4 2
Rheum arthr men	5	4 02	0 65	3 3—4 8
Iron deficiency women	7	3 57	0 67	2 6—4 3
Iron deficiency men	5	4 16	0 83	3 5—5 5
Controls women	21	4 00	0 27	3 3—4 6
Controls men	6	4 27	0 20	4 1—4 6
4 Packed cell volume %				
Rheum arthr women	27	35 26***	2 34	29 5—39 9
Rheum arthr men	5	39 48	6 47	31 2—47 2
Iron deficiency women	7	37 39	6 57	27 1—40 1
Iron deficiency men	5	40 06	8 39	28 5—47 2
Controls women	21	40 13	2 38	35 —45 2
Controls men	7	43 04	3 74	38 8—49 2
5 M C H μμg				
Rheum arthr women	27	28 3**	2 09	25 33
Rheum arthr men	5	28 4	1 14	30
Iron deficiency women	7	25 0	4 58	18 31
Iron deficiency men	5	26 6	3 05	25—3
Controls women	21	30 5	1 67	28—34
Controls men	6	29 3	0 78	8—30
6 M C V μ^3				
Rheum arthr women	27	95 3**	7 8	81—112
Rheum arthr men	5	98 6	5 5	94—108
Iron deficiency women	7	91 3	18 1	0—121
Iron deficiency men	5	97 4	21 3	75—131
Controls women	21	103 4	4 7	93—107
Controls men	6	101 0	6 4	92—10

Table III (cont)

	n	M	SD	Range
7 M C H C %				
Rheum arthr women	27	30 4***	2 3	25—3[illegible]
Rheum arthr men	5	[illegible]9 4	1 1	28—31
Iron deficiency women	7	27 9	2 1	26—32
Iron deficiency men	5	27 8	3 5	24—32
Controls women	21	[illegible] 1	0 9	30—33
Controls men	7	31 3	2 0	28—33
8 Reticulocytes %				
Rheum arthr women	16	1 4***	0 7	0 6—2 8
Rheum arthr men	5	1 7	0 8	0 [illegible]—2 9
Iron deficiency women	7	1 6	1 0	0 7—3 5
Iron deficiency men	5	1 4	0 9	0 6—2 6
Controls women	19	0 8	0 5	0 3—1 8
Controls men	[illegible]	1 2	0 3	0 5—3 3
9 Serum iron µg/100 ml				
Rheum arthr women	27	42 2***	20 3	18—87
Rheum arthr men	5	59 2	26 0	32—90
Iron deficiency women	7	21 1	16 0	10—56
Iron deficiency men	5	50 6	35 7	18—107
Controls women	21	103 0	34 7	46—177
Controls men	7	107 6	6[illegible] 0	54—234
10 T I B C µg/100 ml				
Rheum arthr women	25	279 4**	53 0	206—418
Rheum arthr men	5	279 2	42 9	234—339
Iron deficiency women	5	359 6	81 1	2[illegible]6—484
Iron deficiency men	5	372 8	59 3	304—463
Controls women	15	3[illegible]6 0	41 8	[illegible]46—396
Controls men	5	392 6	74 3	3[illegible]8—514
11 L I B C µ/100 ml				
Rheum arthr women	25	235 8	[illegible]	141—400
Rheum arthr men	5	2[illegible]0 0	60 9	154—280
Iron deficiency women	5	334 6	8[illegible] 1	256—4[illegible]7
Iron deficiency men	5	32[illegible] 2	71 6	255—406
Controls women	15	213 1	49 0	95—293
Controls men	5	277 4	1[illegible] 3	1[illegible]1—431
1[illegible] Saturation of transferrin %				
Rheum arthr women	5	15 [illegible]	7 9	4—38
Rheum arthr men	5	[illegible] 0	1[illegible] 1	10—36
Iron deficiency women	5	7 2	5 0	4—16
Iron deficiency men	5	14 0	10 5	5—31
Controls women	15	3[illegible] 0	10 4	[illegible]—65
Controls men	5	31 6	[illegible]1 6	1[illegible]—65
13 Serum iron rise after oral administration µg/100 ml				
Rheum arthr women	[illegible]3	27 8***	33 7	0—96
Rheum arthr men	5	9 4	50 8	1—120
Iron deficiency women	6	169 0	105 9	80—306
Iron deficiency men	5	[illegible]55 8	74 8	1[illegible]9—357
Controls women	[illegible]1	99 0	54 6	6—196
Controls men	6	52 5	[illegible]5 9	31—99

Table III (cont)

	n	M	SD	Range
14 Haptoglobin, mg/100 ml				
Rheum arthr women	16	292***	109 0	116—420
Rheum arthr men	2	284		267—300
Iron deficiency women	2	83		75—90
Iron deficiency men	1	110		
Controls women	15	89	35 2	50—165
Controls men	3	124		95—160
15 COHb saturation %				
Rheum arthr women	22	0 52***	0 13	0 33—0 83
Controls women	18	0 60	0 12	0 41—0 79
16 Total hemoglobin g				
Rheum arthr women	25	451 9***	63 1	310—605
Rheum arthr men	5	657 0	157 7	505—920
Iron deficiency women	7	420 4	129 0	240—660
Iron deficiency men	5	721 0	143 3	575—930
Controls women	21	530 4	72 8	420—665
Controls men	7	804 1	77 2	714—930
17 Total Hb/kg g				
Rheum arthr women	25	8 0	1 1	6 3—10 4
Rheum arthr men	5	10 5	1 5	9 2—12 9
Iron deficiency women	7	6 7	1 3	4 8—8 3
Iron deficiency men	5	10 9	3 2	7 4—15 8
Controls women	21	8 4	1 5	6 0—11 3
Controls men	7	10 7	1 9	7 7—13 1
18 Total Hb/m g				
Rheum arthr women	25	276 8*	32 1	208 —334
Rheum arthr men	5	377 4	67 7	310—487
Iron deficiency women	7	249 0	53 4	157—282
Iron deficiency men	5	390 6	101 3	279—556
Controls women	21	311 4	39 0	250—380
Controls men	7	419 1	45 6	352—489
19 Total Hb/m body length g				
Rheum arthr women	25	278 8*	38 5	183—359
Rheum arthr men	5	382 6	82 9	294—517
Iron deficiency women	7	255 3	68 5	146—373
Iron deficiency men	5	400 2	92 6	301—551
Controls women	21	320 7	38 6	270—396
Controls men	7	456 1	35 7	421—514
20 Absorption Fe^{59}, % of dose				
Rheum arthr women	15	9 5*	8 6	1—35
Rheum arthr men	3	10 0	8 0	2—18
Iron deficiency women	6	42 8	11 7	30—62
Iron deficiency men	2	41 5		26—57
Controls women	20	18 3	10 5	2—45
Controls men	6	12 7	14 8	0—41

Table III (cont)

	n	M	SD	Range
21 Utilization Fe^{59} % of dose				
Rheum arthr women	25	7 3***	4 5	1—17 6
Rheum arthr men	4	6 9	6 7	3—17
Iron deficiency women	7	33 0	11 7	23—57
Iron deficiency men	5	40 2	13 5	28—62
Controls women	21	15 3	8 5	1—37
Controls men	7	5 4	2 7	2—10
22 Utilization Fe^{59} % of absorbed dose				
Rheum arthr women	15	81	23	41—100
Rheum arthr men	4	62	44	15—100
Iron deficiency women	6	71	23	45—100
Iron deficiency men	5	90	17	61—100
Controls women	20	74	26	17—100
Controls men	6	63	41	9—100

toid arthritis groups compared with the controls but M C H is well within the normal limits given by the text books (69 70)

Statistical comparisons between the two largest groups arthritic and control women show highly significant differences between the means of hemoglobin concentration number of red cells packed cell volume M C H M C V and M C H C (Table III 2—7)

The values for total hemoglobin in these groups are also highly significantly different but related to weight body surface area and height, this significance is reduced This is because the mean weight of the rheumatoid groups is 7 kg less than that of the control group

The values for reticulocytes are significantly higher in the rheumatoid arthritis group than in the controls This might indicate an increased hemolysis in the patient group (compare 20 37 41) However the COHb values are quite normal in the patients with rheumatoid arthritis (non smokers see Table III 15) This indicates that an increased rate of hemolysis is not present among the patients with rheumatoid arthritis included in this study (For a discussion of the COH b-method see 24 and 18) The slightly increased reticulocyte values may be explained at least in part by disturbed maturation or regulation of red cell release from the bone marrow In the present material there is no correlation between the number of reticulocytes and the COHb concentration

There are clear differences between the hematological values of the patients with rheumatoid arthritis and those with iron deficiency (Table III) In the iron deficiency patients the hemoglobin concentration, M C H and M C H C are considerably lower than in the rheumatoid arthritis patients There is thus a real difference in the blood morphology of these two groups

b Serum iron concentration is highly significantly lower in the rheumatoid arthritis patients than in the controls

Table IV

SERUM IRON TOLERANCE TESTS IN PATIENTS WITH RHEUMATOID ARTHRITIS IRON DEFICIENCY AND CONTROLS

	n	Mean value	$\pm\ \varepsilon M$	SD
All patients	83	47	7	61
Patients with serum iron rise 0—99 μg/100 ml	70	25	3	27
Patients with serum iron rise > 100 μg/100 ml	13	167	15	56
All women	59	50	9	66
All men	24	42	10	51
Normal women	21	98	11	55
Normal men	6	53	11	26
Iron deficiency women	6	169	43	106
Iron deficiency men	5	256	33	75

The transferrin values in women with rheumatoid arthritis are significantly lower than in the control group, thus corresponding to Laurell (36) but not to Jeffrey & al (31).

The unbound iron binding capacity (U I B C) is not decreased in patients with rheumatoid arthritis, who thus have no deficiency of iron carrier in their plasma. The saturation percentage of the transferrin is lowest in the iron deficiency group women mean 7 per cent, men mean 14 per cent. These values are within the limits for early and late iron deficiency, given by Bothwell & Finch (7), see Table III 9—12. The women with rheumatoid arthritis have a mean saturation percentage of 15.7 (range 4—38 per cent), and the arthritic men 22 per cent (range 10—36 per cent).

c. *Storage iron* has been determined histochemically in sections of bone marrow. Four out of 22 women with rheumatoid arthritis had no stainable hemosiderin in their bone marrow sections, all of the 5 arthritic men had demonstrable iron in their sternal bone marrow. One of 15 control women had no marrow iron and one of the 5 control men was also negative in this respect. All the subjects with iron deficiency, 5 women and 4 men, were without stainable hemosiderin in their bone marrow sections.

These figures show that most of the patients with rheumatoid arthritis in this study had storage iron as judged from the bone marrow examinations. As all the arthritic patients had cell rich bone marrow and probably also osteoporosis in the sternum where the marrow samples were taken, there was no difficulty in obtaining large representative marrow specimens with easily estimated amounts of iron. In all the control subjects it was much more difficult to get representative marrow specimens and some subjects had to be punctured twice. In this

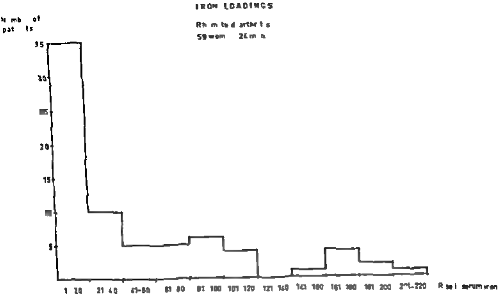

Fig 1
Serum iron tolerance tests in patients with rheumatoid arthritis 59 women and 24 men

respect the subjects with iron deficiency were comparable to the patients with rheumatoid arthritis

The bone marrow as well as the blood picture and transferrin concentration thus shows an essential difference between the patients with rheumatoid arthritis and those with iron deficiency

d The rise in serum iron after oral administration of inert iron (Table III 13) was smaller (P <0 001) in the patients with rheumatoid arthritis compared with the controls while the difference from the iron deficiency group is still more marked

Freireich & al (20) Ebaugh (15) and Bothwell & Finch (7) have demonstrated that both patients with rheumatoid arthritis and subjects with iron deficiency anemia have a more rapid elimination from the plasma pool of injected transferrin bound labelled iron (compare Nilsson 44 who showed the same with non radioactive iron) The very flat oral serum iron tolerance curve in patients with rheumatoid arthritis could be due both to changed absorption from the gastro intestinal tract (decrease of the total amount of iron absorbed or a retardation of iron absorption) and to rapid elimination from the plasma pool

Table IV and Fig 1 show that the rise in serum iron concentration after oral administration of 0 5 g ferrosi lactas is very moderate Only 13 out of 83 patients showed an elevation in the serum iron >100 μg/100 ml which is about the mean increase for the control women (98 μg/100 ml Table III 13) The mean rise of those who increase <100 μg/100 ml is 25 μg/100 ml The mean rise of those who increase >100 μg/100 ml is 167 μg/100 ml

Fig 1 shows that there is a small group of patients with rheumatoid arthritis who

Table IV

SERUM IRON TOLERANCE TESTS IN PATIENTS WITH RHEUMATOID ARTHRITIS IRON DEFICIENCY AND CONTROLS

	n	Mean value	± εM	S D
All patients	83	47	7	61
Patients with serum iron rise 0—99 µg/100 ml	70	25	3	27
Patients with serum iron rise > 100 µg/100 ml	13	167	15	56
All women	59	50	[illegible]	66
All men	24	42	10	51
Normal women	21	98	11	55
Normal men	6	53	11	26
Iron deficiency women	6	169	43	106
Iron deficiency men	5	256	33	75

The transferrin values in women with rheumatoid arthritis are significantly lower than in the control group, thus corresponding to Laurell (36) but not to Jeffrey & al (31)

The unbound iron binding capacity (U I B C) is not decreased in patients with rheumatoid arthritis, who thus have no deficiency of iron carrier in their plasma The saturation percentage of the transferrin is *lowest in the iron deficiency group* women mean 7 per cent, men mean 14 per cent These values are within the limits for early and late iron deficiency given by Bothwell & Finch (7), see Table III 9—12 The women with rheumatoid arthritis have a mean saturation percentage of 15 7 (range 4—38 per cent), and the arthritic men 22 per cent (range 10—36 per cent)

c *Storage iron* has been determined histochemically in sections of bone marrow Four out of 22 women with rheumatoid arthritis had no stainable hemosiderin in their bone marrow sections, all of the 5 arthritic men had demonstrable iron in their sternal bone marrow One of 15 control women had no marrow iron and one of the 5 control men was also negative in this respect *All* the subjects with iron deficiency 5 women and 4 men, were without stainable hemosiderin in their bone marrow sections

These figures show that most of the patients with *rheumatoid arthritis in this study* had storage iron as judged from the bone marrow examinations As all the arthritic patients had cell rich bone marrow and probably also osteoporosis in the sternum where the marrow samples were taken there was no difficulty in obtaining large representative marrow specimens with easily estimated amounts of iron In all the control subjects it was much more difficult to get representative marrow specimens and some subjects had to be punctured twice In this

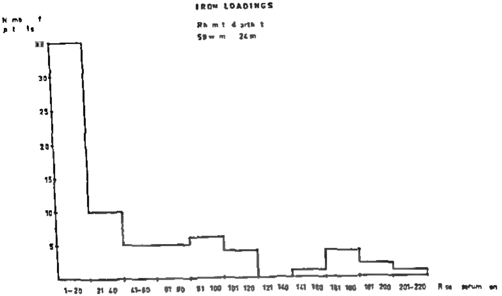

Fig 1
Serum iron tolerance tests in patients with rheumatoid arthritis 59 women and 24 men

respect the subjects with iron deficiency were comparable to the patients with rheumatoid arthritis

The bone marrow as well as the blood picture and transferrin concentration thus shows an essential difference between the patients with rheumatoid arthritis and those with iron deficiency

d The rise in serum iron after oral administration of inert iron (Table III 13) was smaller (P <0 001) in the patients with rheumatoid arthritis compared with the controls while the difference from the iron deficiency group is still more marked

Freireich & al (20) Ebaugh (15) and Bothwell & Finch (7) have demonstrated that both patients with rheumatoid arthritis and subjects with iron deficiency anemia have a more rapid elimination from the plasma pool of injected transferrin bound labelled iron (compare Nilsson 44 who showed the same with non radioactive iron) The very flat oral serum iron tolerance curve in patients with rheumatoid arthritis could be due both to changed absorption from the gastro intestinal tract (decrease of the total amount of iron absorbed or a retardation of iron absorption) and to rapid elimination from the plasma pool

Table IV and Fig 1 show that the rise in serum iron concentration after oral administration of 0 5 g ferrosi lactas is very moderate Only 13 out of 83 patients showed an elevation in the serum iron >100 μg/100 ml which is about the mean increase for the control women (98 μg/100 ml Table III 13) The mean rise of those who increase <100 μg/100 ml is 25 μg/100 ml The mean rise of those who increase >100 μg/100 ml is 167 μg/100 ml

Fig 1 shows that there is a small group of patients with rheumatoid arthritis who

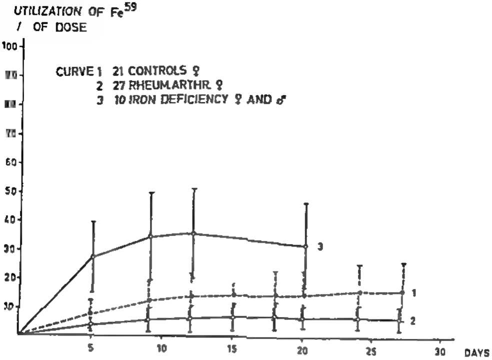

Fig. 2.
Erythrocyte utilization curves.

have an elevation in serum iron concentration of > 100 μg/100 ml; these are probably cases with a certain degree of iron deficiency.

e. Iron absorption, measured with Fe^{59} (Table III: 20) showed probably significantly lower values in the women with rheumatoid arthritis (mean 9.5 per cent absorption of dose) than in their control group (mean 18.3 per cent). In the iron deficient subjects the values for Fe^{59} absorption are materially higher (women mean 42.8 per cent, men mean 41.5 per cent of the dose).

Two patients with rheumatoid arthritis (cases 14 and 15, Table I) were heavily overloaded with iron at the time of the absorption test with Fe^{59}. Case 14 had received altogether 3 g of iron dextrin intravenously during the 2 months preceding the absorption test. The absorption value was zero and utilization 1 per cent of the test dose in the circulating erythrocytes. Case 15 had received ferrosuccinate tablets 0.9 g daily for 3 weeks immediately before the absorption test, and two bottles of blood (800 ml) two days before the test was administered. She absorbed 5 per cent and utilized 3.5 per cent of the test dose in her erythrocytes after 14 days. According to Conrad & Crosby (12) and Charlton & al. (10) the intestinal mucosa of these two patients was blocked and the iron absorption was impaired, in case 14 almost to zero. These two cases have of course been excluded from the statistical analysis concerning the absorption test.

f. The utilization of Fe^{59} in circulating erythrocytes 14—21 days after the administration of the test dose shows the same tendency as the absorption pattern (Table III: 21, 22, Fig. 2). The difference between the rheumatoid arthritis women and their controls is *highly significant*.

Table V

CORRELATION ANALYSIS BETWEEN SOME VARIABLES IN PATIENTS WITH RHEUMATOID ARTHRITIS AND CONTROLS (WOMEN)

The degree of significance of the r values is indicated

Variables studied	Controls		Rheumatoid arthritis patients	
	Number of cases	r	Number of cases	r
Rise in serum, inert loading TIBC	15	0.24	22	−0.41
Absorption Fe^{59} TIBC	14	0.60*	17	0.28
Erythrocyte utilization TIBC	15	0.60*	25	0.16
Rise in serum iron, inert loading UIBC	15	0.25	22	−0.12
Absorption Fe^{59} UIBC	14	0.5*	16	0.17
Erythrocyte utilization Fe^{59} UIBC	15	0.39	25	0.09
Absorption Fe^{59} Erythrocyte utilization of Fe^{59}	20	0.60**	17	0.69**
Rise in serum iron inert loading Saturation of transferrin	15	−0.14	22	0.46*
Absorption Fe^{59} Saturation of transferrin	14	−0.17	17	0.08
Erythrocyte utilization Fe^{59} Saturation of transferrin	15	−0.[illegible]8	[illegible]5	0.13
Absorption Fe^{59} Rise in serum iron inert loading	[illegible]0	0.07	15	0.40
Total acidity in histamine test Absorption of Fe^{59}			15	0.30

The utilization in the red blood cells as a percentage of the amount absorbed is about the same in all three groups of subjects from 62 to 90 per cent. It is not lower in the arthritic patients than in the iron deficient and normal subjects. Thus there does not seem to be any defect in iron incorporation into the circulating erythrocytes of the rheumatoid arthritis patients in this study. The same finding has been reported by Freireich & al (20) and Weinstein (65) who found normal incorporation of intravenously injected transferrin bound labelled iron.

g. The histamine test revealed histamine fast achlorhydria in the female arthritic group in 9 out of 25 cases, in the female iron deficient group in 3 out of 7 cases and in none of 11 control women. For eight control women the Diagnex test was positive. There was no correlation between the absorption of Fe^{59} and total acidity (Table V) in accordance with Bothwell & Finch (7) but contrary to Goldberg & al (23).

h. Correlation analysis (Table V). An extensive correlation analysis has been performed between variables with possible interrelations. Moreover the female rheumatoid arthritis group has been subdivided into low and high clinical activity according to Shetlar & al (50). No significant differences were found concerning the absorp-

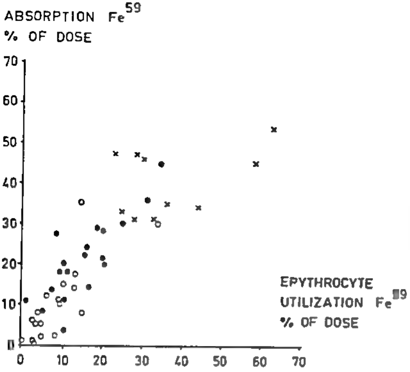

Fig 3
Relation between the absorption of radioiron and the incorporation of radioiron in circulating erythrocytes 2 weeks after the administration of the dose

18 rheumatoid arthritis women o
19 control women •
10 sideropenic patients (women and men) x
$r = 0.81$
$t = 9.33$
$P = < 0.001$
$y = 4.46 + 0.884\,X$

tion and utilization of iron in the low and high activity groups (In another paper (60) in which we have analyzed a larger material of rheumatoid arthritis patients with respect to clinical activity, significant correlations were found between clinical activity and E S R, hemoglobin concentration, red blood cell values and serum iron concentration but not between clinical activity and M C H)

In this material there was no correlation between the transferrin and U I B C or the saturation percentage of the transferrin versus the rise in serum iron in the oral tolerance test absorption and utilization of Fe^{59} (Table V) The absorption and utilization of Fe^{59} are significantly intercorrelated in the female rheumatoid arthritis and control groups When the values of all three groups are analyzed together, absorption and utilization of Fe^{59} are highly significantly correlated (Fig 3 Table V)

The absorption of Fe^{59} and the rise in serum iron in the tolerance test are not significantly intercorrelated within the groups (probably significant in the female iron deficiency group) but the three groups together show a significant ($P < 0.001$) correlation (Table V, compare Jeffrey & co workers 31 who found the same relation in their patients with rheumatoid arthritis)

The absorption and utilization of Fe^{59} and the results from the peroral non radioactive iron absorption test were not correlated to the total hemoglobin blood volume plasma volume or red cell volume nor was there any correlation when these last variables were related to the body parameters weight surface area and height These analyses were made for the two largest groups female arthritic patients and their controls (The blood plasma and red cell volumes have also been analyzed Chapter IV)

Discussion

a Hematological data

The analysis of hematological data and bone marrow iron shows that there is a clear cut difference between the patients with rheumatoid arthritis and those with iron deficiency. In the present material of rheumatoid arthritis patients iron deficiency was thus excluded on the basis of anamnesis and the above mentioned criteria. This is in contrast to the material of Jeffrey & al (31) which included a number of patients with iron deficiency.

Forty per cent of the present women with rheumatoid arthritis had had some form of iron treatment during the years before the iron absorption test (Table I) but only two patients had received such therapy in the year immediately preceding the test as mentioned above. In a material of 300 rheumatoid arthritis patients from the Stockholm area in which patients with complicating diseases had been excluded on the basis of history and routine clinical examination signs of iron deficiency with low M C H were not very common (60) which is in accordance with Nilsson's material (44) but in contrast to the material of Jeffrey & al (31). Patient materials from different countries certainly display different frequencies of iron deficiency probably due to differences in medical treatment as well as in nutrition. These factors have not been analysed in the present study.

For most of the hematological variables the women have lower means well in agreement with Nilsson (44) and many authors cited by him and Jeffrey (29). The tendency is the same in the iron deficiency groups and controls. In the present material too there seems to be a clear difference between the sexes with lower values in women (cf Table III).

b Absorption of iron The absorption of Fe^{59} was lower in the arthritic group compared with the controls. The mean for the female rheumatoid arthritis patients was 9.5 per cent of the Fe^{59} dose which is about half the mean for the female controls (18.3 per cent).

Owing to the large standard deviations the differences between the means are not more than probably statistically significant. The present finding agrees with that of Roberts & al (48) who reported impaired Fe^{59} absorption in 12 rheumatoid arthritis patients compared with normal controls. Raymond & al (47) found that 5 patients out of 9 had subnormal absorption of radioiron.

Although the present material of arthritic patients iron deficiency cases and controls is rather limited in size it has been carefully investigated with respect to hematological data relevant to the problems of iron absorption and utilization. As pointed out by Bothwell & Finch (7) and Bainton & Finch (6) the degree of iron deficiency must be assessed with great care in a patient material of this kind. Judging from the transferrin saturation values, some of the arthritic patients in the present material could have a simple iron deficiency. However when the hematological and marrow iron data are also taken into account these patients correspond more closely to the group characterised by the term iron deficient erythropoiesis suggested by Bainton & Finch (6) patients with bone marrow iron rather low percentage saturation of transferrin normochromic or slightly hypochromic erythrocytes. This group also includes the anemia of infection.

When evaluating the anemia of rheumatoid arthritis, care must be taken to rule out other diseases or complications which in themselves may cause iron deficiency anemia Twenty six of the 27 female rheumatoid arthritis patients had salicylate therapy ad libitum, usually 3—4 g daily It is thus not possible to compare iron absorption and utilization in patients with and without salicylate therapy in this material Izak & al (27) report that salicylates exerted a depressing influence on the serum iron in 9 subjects, including one patient with rheumatoid arthritis In two cases studied with Fe^{59}, salicylate administration caused no impairment of iron absorption and utilization Wood & Wilson (72) studied 150 patients with rheumatoid arthritis and found no correlation between anemia and the amount of occult blood loss caused by aspirin However in a small number of the their arthritic patients the anemia was considered to be due primarily to aspirin induced bleedings in the gastro intestinal tract In the present series of patients with rheumatoid arthritis, regular controls of occult blood loss were always negative Besides in the Empire Rheumatism Council s (17) multicentral controlled trial comparing cortisone and acetylsalicylic acid in the long term treatment of rheumatoid arthritis there was at the end of the third year a significant elevation of the mean hemoglobin concentration for the salicylate group, compared with the starting value In our opinion this result is a strong argument against salicylate induced gastro intestinal bleedings as a cause of anemia in patients with rheumatoid arthritis

Hallberg & Solvell (25) have demonstrated a rapid initial and a subsequent slower absorption period for iron in humans Wheby & Crosby (66) and Wheby & al (67), working with rats and a whole body monitoring technique, demonstrated two absorption components an initial period of up to two hours duration, with rapid absorption of 60—80 per cent of the total iron absorption The remaining absorption was slower, with a duration of 10—20 hours In our patients with rheumatoid arthritis, the flat serum iron tolerance curves (even when blood samples were drawn at short intervals during the first hour) and the decreased total iron absorption in the Fe^{59} tests could be interpreted as a defect in the intestinal mucosa function during the first rapid absorption period

However, this defect does not seem to precipitate iron deficiency in these patients

The absorption of tagged iron in these rheumatoid arthritis patients has been found to be uncorrelated to the gastric production of hydrochloric acid (cf Bothwell & al 7 and Goldberg & al, 23) Other factors in the gastric secretion might be of importance or possible as an explanation of the decreased iron incorporation in the arthritis patients (see e g Koepke & Stewart s (33) iron binding factor in the gastric juice) According to Davis & Badenoch (13) Davis & Biggs (14) and Bothwell (8), the iron absorption is considerably elevated but the iron utilization is decreased in patients with pancreatic damage No analyses of the pancreatic function have been made in our subjects but the decreased iron absorption and normal iron utilization do not make pancreatogenic anemia probable in the patients with rheumatoid arthritis

The influence of the dietary intake of food, vitamins and minerals has not been analysed in our material According to Eising (16), the frequency of faulty dietary habits (vitamins, minerals) is high in pa

tients with rheumatoid arthritis and a small proportion of these patients have inadequate intake of protein which might be responsible for impaired iron absorption (Kroe & al 33)

c *The utilization* of the absorbed iron in patients with rheumatoid arthritis does not seem to be lower than in the groups with iron deficient subjects and the controls Seven out of 17 women with rheumatoid arthritis had 100 per cent utilization of the absorbed dose This is in accordance with the results of Freireich & al (20) and Weinstein (65) who administered tracer iron intravenously Results from a group of patients with rheumatoid arthritis studied with intramuscularly injected Fe^{59} labelled iron sorbitol-citric acid (Jectofer Astra Sodertalje Sweden) revealed the same incorporation in the circulating erythrocytes after 14 days — 28 per cent — as in a control group utilizing 26 per cent as a mean (59) These studies together with those cited (20 65) suggest that a defect in iron incorporation in the red cells reaching the circulation is not of major importance in the genesis of the anemia of rheumatoid arthritis

However Jeffrey & al (31) often found incomplete utilization of the absorbed iron in rheumatoid arthritis patients including those with a considerable anemia Data reported by Roberts & al (48) accord with Jeffrey s However the methods used in the present study and in the papers cited are too crude to settle this question

In this and the cited studies there has been no investigation concerning the reutilization of the iron originating from red cell destruction In a recent paper Haurani & al (26) have demonstrated a defective reutilization of this iron and two cases of rheumatoid arthritis were included in their study

The most striking finding in our investigation seems to be that the absorption is lower in rheumatoid arthritis subjects compared with normal persons and that the utilization calculated as a percentage of the dose absorbed is not lower than that of the control or iron deficiency groups

The fundamental differences between patients with rheumatoid arthritis and iron deficient subjects have also been demonstrated

To judge from the endogenous carbon monoxide determinations there are no signs of hemolysis in the present material of patients with rheumatoid arthritis The haptoglobin determinations give little information on this point as patients with active rheumatoid arthritis always have considerably elevated values (Table III 14)

Summary

Patients with active rheumatoid arthritis have been compared with iron deficient and normal subjects in respect of hematological data including bone marrow storage iron iron absorption and utilization hemolysis has been evaluated by the carbon monoxide method and reticulocyte counting

The patients with rheumatoid arthritis had a true anemia with decreased hemoglobin concentration (—17 per cent compared with the controls) and decreased amount of total hemoglobin (—15 per cent compared with the controls) The number of erythrocytes was decreased and the erythrocyte indices M C H and M C H C were reduced indicating slight hypochromia and slight microcytosis

Serum iron and transferrin concentrations were reduced compared with the controls The unbound iron binding capacity was not

reduced, and the mean saturation percentage for the rheumatoid arthritis group was between the values for the normal and the iron deficient groups

The COHb estimates were normal in the rheumatoid arthritis group This negates any significantly increased breakdown of hemoglobin The slightly increased reticulocyte values may be explained at least in part by disturbed maturation or regulation of red cell release from the bone marrow

The bone marrow contained histochemically demonstrated storage iron in 23 out of 27 patients with rheumatoid arthritis

The iron absorption measured with Fe^{59} was decreased ($0.05 > P > 0.01$) in patients with rheumatoid arthritis compared with the controls

The utilization of Fe^{59} paralleled the absorption but could not be used as an absorption test in the subjects investigated and presented here When calculated as a percentage of the absorbed dose, the utilization in the patients with rheumatoid arthritis was close to that found in the control group

The correlation between several of the investigated variables and clinical activity has been analyzed

This study has been supported with grants from *Konung Gustaf V s 80arsfond, Riksföreningen mot Reumatism* and *Karolinska institutet*

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CHAPTER III

DISTRIBUTION AND UTILIZATION OF Fe^{59}-LABELLED IRON-SORBITOL-CITRIC ACID (JECTOFER) IN PATIENTS WITH RHEUMATOID ARTHRITIS AND HEALTHY CONTROLS

O Strandberg

The many works on iron therapy experiments in the anemia of rheumatoid arthritis have been summarized by Alexander & Duthie (2) Most investigators are agreed that in spite of hypoferremia and a slightly lowered erythrocyte index (MCH, MCHC) the anemia seldom reacts to peroral iron unless there is a real iron deficiency with microcytosis, elevated serum transferrin concentration and empty iron stores Collins (9), Nilsson (30) Sinclair & Duthie (38 39), Ross (35) and Jeffrey (18, 19) have all noted that the anemia is refractory to orally administered iron

The effect of 1 gram doses of saccharated oxide of iron has been studied by Sinclair & Duthie (38 39) Ross (35) Jeffrey (18 19) Millard & Barber (27) and Mc Crea (25) Richmond & co workers (34) gave a larger dose (5 grams) in a controlled study to patients with rheumatoid arthritis, who were compared with a group not given iron therapy but with rheumatoid arthritis of comparable clinical activity They reported that the anemia was reduced in all cases At the same time, there was clinical improvement with a lowering of the mean ESR, an increase of the functional capacity and a decrease of the clinical activity The increase in hemoglobin values after the administration of saccharated oxide of iron showed no correlation with the initial concentration of marrow iron, the degree of anemia, MCHC or the clinical activity of the disease

Studies of the iron sorbitol metabolism in normal and iron deficient patients have been published by Wetherley Mein & al (53) and in iron deficient patients by Pringle & al (31) The therapy of iron deficiency patients has been described in several publications dealing with iron sorbitol (6 36 42, 21) Most aspects of iron sorbitol were discussed in detail at a conference held in Worcester (Mass, U S A) in September 1962 (11) Up to the autumn of 1965, no investigations appear to have been published on the iron sorbitol metabolism in patients with rheumatoid arthritis

Previous reports (30 13) and own results (45 46, 47) indicate that the hemoglobin concentration in the circulating erythrocytes may be moderately reduced in patients with active rheumatoid arthritis This is evident from slightly reduced MCH and MCHC values and may be interpreted as an iron deficient erythropoiesis (7) even though marrow iron stores are found in approximately 60 per cent of patients with rheumatoid arthritis (25 33), marrow iron could be demonstrated histochemically in 47 of 57 (72 per cent) patients examined personally (Johansson & Strandberg to be published)

It has been shown by Fielding (11) and Wohler (55 56) that iron sorbitol which has a low molecular weight (< 5 000 Eriksson cited by Svärd & Lindvall 49) is distributed differently among the organs in question compared to high molecular preparations (saccharated oxide of iron iron dextran iron dextrin M = 180 000—230 000) Fielding (12) has noticed an unusually rapid erythropoietic reaction after the administration of iron sorbitol to patients with iron deficiency anemia and suggests that iron in this form may be directly available from the complex molecule to the marrow receptor Wohler (56) has also put forward this idea

This paper is concerned with two main problems

1 Is there any difference in the degree to which intramuscularly administered radio iron sorbitol is utilized by circulating erythrocytes in patients with rheumatoid arthritis compared with normal controls and previously published materials of iron deficiency anemia (53 31)?

2 Are there quantitative or temporal differences between patients with rheumatoid arthritis and controls in respect of the distribution of iron sorbitol in liver spleen and bone marrow elimination from the injection site and urinary excretion?

To this end a group of patients with rheumatoid arthritis and a group of normal cases have been examined with Fe^{59} labelled iron sorbitol (Jectofer)

Material

a Patients with rheumatoid arthritis

Seven women and four men with active rheumatoid arthritis (3 4 5) clinical activity II—IV (37) and a mean age of 48 0 years (range 16—64)

b Controls

Two women and four men They were subjectively healthy had not donated blood had a normal blood picture ESR and serum protein pattern according to paper electrophoresis examinations The bone marrow was examined in four cases and found to be cytologically normal

Because the groups are so small the results for women and men have been combined

In addition to the above cases an examination was made in a women aged 50 with a severe life long iron deficiency anemia due to a malabsorption syndrome

Laboratory methods

a Hemoglobin concentration was determined as alkaline oxyhemoglobin in a Beckman B spectrophotometer at 540 mm Standardisations with determination of the oxygen capacity of the blood were made at regular intervals

b Red blood corpuscles were analysed with an electronic cell counter (Celloskope Lars Ljungberg & Co Stockholm)

c The volume of packed red cells was determined with the International hematocrite centrifuge type MB (International Equipment Boston Mass U S A) which performs 11 500 r p m Well mixed venous blood from heparinised tubes was centrifuged for 10 minutes and duplicate determinations were carried out Correction for trapped plasma (8) was made The factor used was 1 3 % according to Garby & Vuille (15)

d ESR The Westergren method was used one hour value No correction was made for anemia

e *Serum iron concentration* Double determinations with the orthophenantroline method according to Agner (1)

f *Transferrin* Surplus iron, absorbed on an ion exchanger, was added and the iron binding capacity was determined with Agner's serum iron method These analyses as well as those for serum iron were performed at the Central Chemical Laboratory, Karolinska sjukhuset

g *Total hemoglobin* was determined by the alveolar CO method of Sjöstrand (40, 41), with modifications (54, 22, 23) Duplicate determinations were made in every individual examined, at the department of Clinical Physiology, Karolinska sjukhuset

All hematological analyses were performed as duplicate determinations on well mixed heparinised venous blood

h *Bone marrow iron* Analyses were performed (a) with pottassium ferrocyanide staining of sectioned bone marrow specimens, according to Rath & Finch (32), and (b) chemically after defatting and hydrolysis with hydrochloric acid (44)

i *Fe^{59} labelled iron sorbitol,* prepared on a laboratory scale by a standardised production technique, contained 50 mg iron and approximately 10 μg Fe^{59} per ml iron sorbitol The tagged material was controlled with electrophoresis and gel diffusion by the manufacturer and displayed properties identical with the commercial product Jectofer (AB Astra, Sodertalje, Sweden) The physical and chemical properties of non radio active iron sorbitol have been described by Lindvall & Andersson (24), Svard (48) Svard & Lindvall (49)

k *Measurement of radioactivity* The labelled iron sorbitol preparation was injected together with non radioactive iron sorbitol as carrier, in the deltoid muscle of the left shoulder This site was chosen so that the activity in the bone marrow above the sacrum could be measured without backgorund disturbance (53) The dose varied between 10 and 15 μC Fe^{59} and the volume between 2 and 4 ml of the injected preparation

The radioactivity above the injection site the heart, liver, spleen and sacrum was measured with a Nuclear Chicago spectrometer computer discriminating for the energy peaks of Fe^{59} 1 1 and 1 3 Mev The measuring crystal was a 2 by 2 ins thallium activated NaI crystal screened with a lead casing it was easy to site over the organ and reproducible measuring results were obtained after some practice External measurements were made frequently during the first 6 hours then daily for one week and every other day during the second week after administration of the experimental dose Five ml samples of blood and urine were measured in an ordinary well crystal Tracerlab P 20 B W, connected to a Versamatic II Scaler Spectrometer A fully automatic sample changer was used The counting efficiency for Fe^{59} in samples of blood and urine was 20 per cent with this equipment Ten thousand impulses were counted on every sample and double samples were measured so that the accuracy was within $\pm$ 2 per cent (51) The amount of radioactivity was calculated by simultaneous comparison with a known standard

The radioactivity in blood and urine was expressed as a percentage of a given dose of Fe^{59} over different organs in counts per minute per given amount of Fe^{59} expressed in μC (20)

The errors of method for the hematological laboratory methods used have been reported in previous papers (46 47)

Table I

MEANS OF HEMATOLOGICAL DATA IN PATIENTS WITH RHEUMATOID ARTHRITIS AND CONTROLS AND ONE PATIENT WITH IRON DEFICIENCY ANEMIA

	Controls			Rheumatoid arthritis			Iron deficiency
	n	Mean	S D	n	Mean	S D	
Hemoglobin conc., g/100 ml	6	13 4	1 3	11	10 8	1 4	9 0
Red blood cells mill	6	4 4	0 5	11	3 9	0 5	4 1
Packed cell volume %	[illegible]	40 8	3 6	11	34 7	3 8	31 4
MCH $\mu\mu g$	6	30 4	1 6	11	27 8	3 3	22 0
MCHC, %	6	32 7	1 1	11	31 1	2 3	28 9
MCV μ^3	6	9_8	3 8	11	89 7	10 3	76
Total hemoglobin g	6	636	12?	11	461	101	145
Serum iron, μg/100 ml	6	87 3	34	11	48 3	37	35
TIBC, μg 100 ml	6	3?_	39	11	96	34	346
Saturation % of transferrin	6	27	12	11	16	11	10
Bone marrow iron, mg/100 g (marrow without fat)	4	18	9	8	20	15	
ESR mm/1 hour	6	7 3	8 0	11	39 6	30 1	37

f Statistical methods Generally accepted statistical methods were used with calculation of means and standard deviations Student's t test for small samples was used to determine the level of significance (43)

Results

a Hematological data (Table I) Compared with the controls the patients with rheumatoid arthritis have an anemia that is practically normochromic with mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration within normal limits The mean corpuscular volume is also within normal limits in the patients with rheumatoid arthritis so that their anemia may be characterised as normocytic. In these patients the total hemoglobin is significantly reduced (by 27 per cent in relation to the controls) and the hemoglobin concentration is also lower (by 20 per cent not significant) The analyses of bone marrow iron show that iron stores are generally present in the arthritic patients Hemosiderin was demonstrated in the bone marrow sections of 8 out of 9 patients with rheumatiod arthritis while all 4 of the controls examined had histochemically demonstrable iron in their bone marrow The difference between the two groups

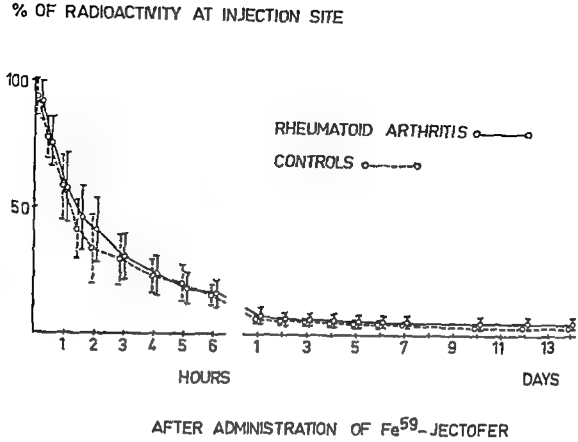
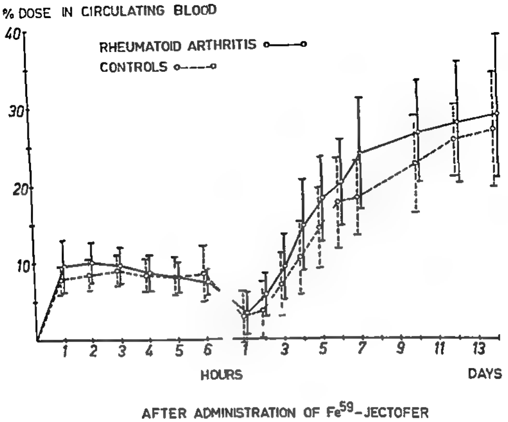


Fig 1
Eleven patients with rheumatoid arthritis and 6 controls
Elimination of labelled Jectofer from the injection site
Means and one standard deviation of the groups are indicated

means for serum iron concentration is statistically significant at the 5 per cent level

b Elimination of Fe^{59} labelled iron sorbitol from the injection site (Fig 1) As in several previous papers (cf e g 31, 53), there was a rapid and almost complete elimination of the labelled preparation from the injection site The mean amount of the dose administered remaining at the injection site was, after 6 hours approx 16 per cent in both groups after 24 hours approx 6 per cent in both groups and after 14 days 4 5 per cent in the arthritis group and 2 7 per cent in the control group The corresponding figures for the iron deficiency patient were after six hours 11 per cent 24 hours 6 5 per cent and after 10 days 2 per cent

c Utilization of Fe^{59} in circulating erythrocytes (Fig 2) During the first 6 hours only plasma radioactivity was measurable After 24 hours there was no detectable plasma radioactivity while radioactivity could already be detected in circulating red blood cells It appears that the utilization of Fe^{59} occured equally rapidly in both groups The degree of utilization was somewhat higher in the patients with rheumatoid arthritis (mean = 28 4 per



Fig

Eleven patients with rheumatoid arthritis and 6 controls Utilization of labelled Jectofer in the circulating red cells

Indications as in fig 1

cent) than in the controls (mean = 26 4 per cent) but the difference is not significant ($P > 0.05$) The iron deficiency patient utilized 37 5 per cent of the dose for incorporation in circulating erythrocytes

d Measurements over the liver Fig 3 shows that incorporation of Fe^{59} in this organ started during the first few hours after the injection of iron sorbitol and continued for about 3 days In the arthritis group the measurements remained at about the same level until the 9th day after which the radioactivity fell indicating elimination of radioiron from the organ (and reticuloendothelial system) The normal cases tended to eliminate the radioactivity somewhat faster from the liver than did the patients with rheumatoid arthritis (cf Fig 3 4 5) and so did the patient with iron deficiency (Fig 6) It is interesting that the patient with rheumatoid arthritis who had the poorest utilization of Fe^{59} in red blood cells (14 per

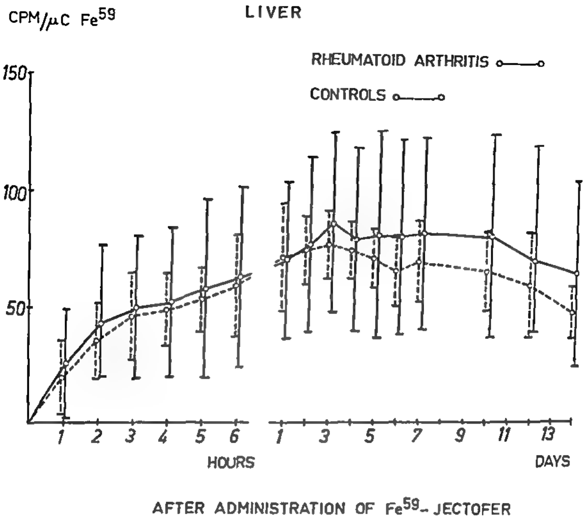


Fig 3
Eleven patients with rheumatoid arthritis and 6 controls
Radioactivity curves measured over the liver
Indications as in fig 1

cent of the dose) had the highest activity of all the cases examined over the liver spleen and bone marrow (Fig 7) This patient displayed the most bone marrow iron in the entire series and her liver and spleen were roentgenologically enlarged An arthritic patient with no demonstrable bone marrow iron displayed little activity in the liver and spleen but a high percentage utilization in circulating red blood cells (47 per cent of the dose after 14 days) No regular correlation could be demonstrated between the amount of storage iron and the utilization of radioiron in red blood cells (see below)

e Measurements over the spleen (Fig 8) revealed much the same pattern as the measurements over the liver but owing to the smallness of the spleen the measurements curves were not so even (cf Fig 7) No

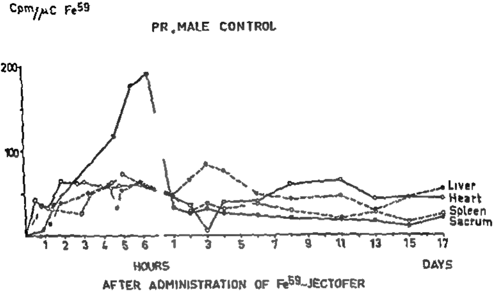


Fig 4
Counting patterns over different body sites after administration of labelled Jectofer male control subject

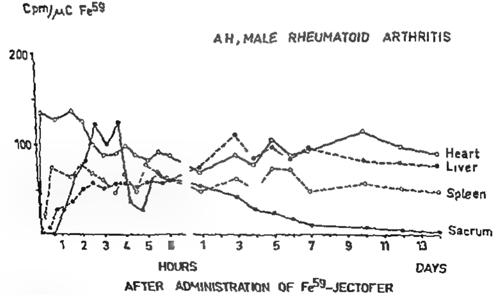


Fig 5
Counting patterns over different body sites after administration of labelled Jectofer man with rheumatoid arthritis

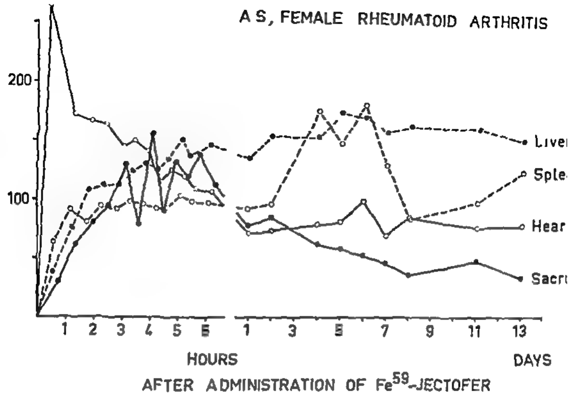
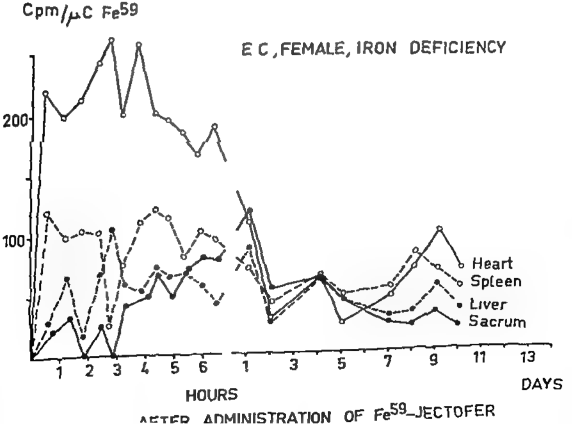


Fig 6
Counting patterns over different body sites after administration of labelled Jectofer woman with iron deficiency



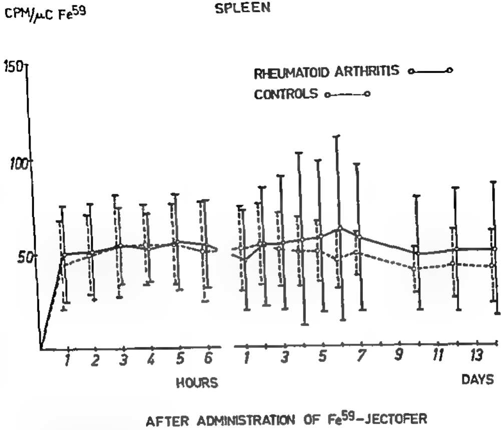


Fig 8
Eleven patients with rheumatoid arthritis and 6 controls
Radioactivity curves measured over the spleen
Indications as in fig 1

discernible difference in the activity in the spleen was found between the two groups

f Measurement over the bone marrow (sacrum) (Fig 9) Here there was a rapid rise during the first 24 hours and then a falling tendency after a further day No difference could be found between the patterns for the two groups The elimination of radioactivity was noticeably more rapid from bone marrow than from liver and spleen The fall in the bone marrow curve coincided with the rise in the curve for utilization in erythrocytes (Fig 2)

g Excretion of Fe^{59} in urine (Fig 10) The mean excretion of the radioiron dose administered was 33 5 per cent in the arthritic group and 29 6 per cent in the control group The iron deficiency patient excreted 21 7 per cent The excretion occurred chiefly during the first 24 hours with inconsiderable amounts thereafter The data agree with those previously reported (6 53 31)

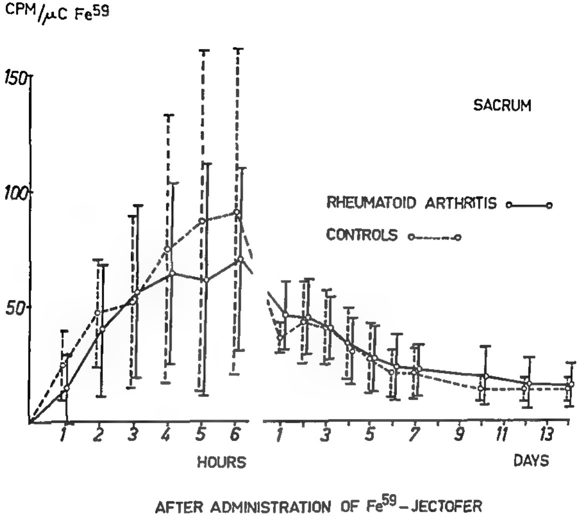
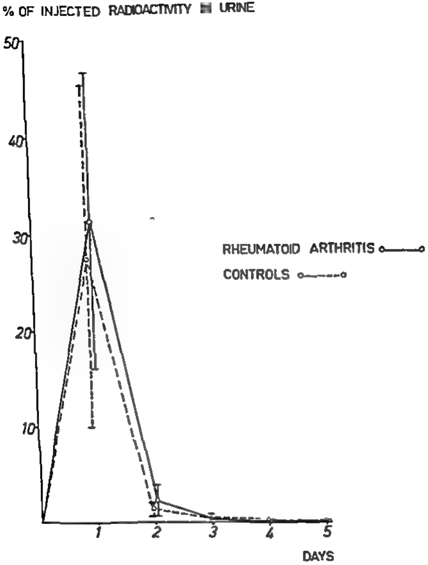


Fig 9
Eleven patients with rheumatoid arthritis and 6 controls
Radioactivity curves measured over the bone marrow (sacrum)
Indications as in fig 1

b The serum iron concentration during the experiment (Figs 11, 12, 13) was analysed at frequent intervals The iron binding capacity, determined on samples taken immediately before the experiment was exceeded during the first hours in all cases examined In most cases the serum iron concentration was above TIBC from the 1st to the 6th hours inclusive Initial levels were regained as a rule after 24 hours In none of the tested subjects were there any signs of iron poisoning or other toxic symptoms ascribable to overstepping the iron binding capacity None of the subjects used iron preparations during the period in question (cf Scott 36)

c Correlation analysis Table II shows that in this relatively small material no definite correlations could be demonstrated between utilization of iron sorbitol Fe^{59} in circulating erythrocytes after 14 days on the one hand and hemoglobin concentration



AFTER ADMINISTRATION OF Fe^{59}–JECTOFER

Fig. 10
Ten patients with rheumatoid arthritis and 6 controls
Urine excretion of labelled Jectofer
Indications as in fig. 1

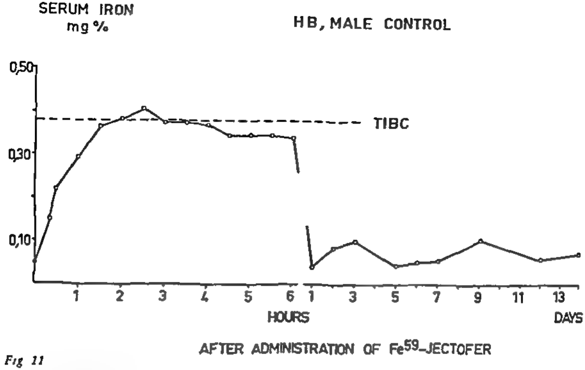


Fig 11
Serum iron concentration during the test period The transferrin concentration at the beginning of the trial is indicated
Male control subject

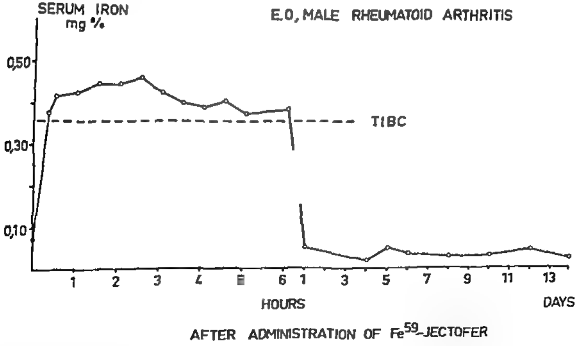


Fig 12
Serum iron concentration during the test period The serum transferrin concentration at the beginning of the trial is indicated
Man with rheumatoid arthritis

Table II

Eleven patients with rheumatoid arthritis and 6 control subjects Correlation between the utilization of labelled iron sorbitol 2 weeks after administration of the test dose (dependent variable) and various independent variables

Independent variable	n	r
Hemoglobin concentration		
Controls	6	−0.57
Rheumatoid arthritis	11	0.47
Contr + Rheum arthr	17	0.01
Total hemoglobin		
Controls	6	−0.87**
Rheumatoid arthritis	11	0.41
Contr + Rheum arthr	17	−0.10
Red blood cells		
Controls	6	−0.74
Rheumatoid arthritis	11	0.49
Contr + Rheum arthr	17	0.01
MCHC		
Controls	6	0.04
Rheumatoid arthritis	11	0.26
Contr + Rheum arthr	17	0.15
Serum iron concentration		
Controls	6	−0.67
Rheumatoid arthritis	11	0.54
Controls + Rheum arthr	17	0.14
T[illegible] concentration		
Controls	6	0.45
Rheumatoid arthritis	11	0.02
Controls + Rheum arthr	17	0.10
Saturation of transferrin		
Controls	6	−0.85*
Rheumatoid arthritis	11	−0.01
Controls + Rheum arthr	17	−0.21
Bone marrow iron		
Control	4	−0.75
Rheumatoid arthritis	8	−0.56
Controls + Rheum arthr	12	−0.56

total hemoglobin red blood cell count MCHC serum iron concentration and bone marrow iron on the other

k Side effects All subjects experienced an aching pain at the injection site during the first minutes after the injection of iron sorbitol the pain started to fade after about 2 minutes and had disappeared as a rule after 10 minutes.

There was swelling and a slight dark discolouration around the site of the injection in 2 cases probably owing to leakage of Jectofer from the puncture. The larger of these discolourations was 3—4 cm in circumference At a check up 6 months later neither of these two patients had any discolouration left.

The principal results are summarized in Table III

Discussion

a Degree and type of anemia and its significance for the utilization of iron sorbitol

Pringle & al (31) report that patients with iron deficiency had a mean utilization of 37.5 ± 7.3 per cent of the injected dose of Fe^{59} labelled iron sorbitol Wheterley Mein & al (53) published 10 cases of which 3 had normal blood values In these 3 cases the utilization of Fe^{59} was 33.0 per cent 27.8 per cent and 26.9 per cent of the dose 3 of the other cases had iron deficiency and utilized 41.7 per cent 49.6 per cent and 66.5 per cent of the dose Mc Curdy (26) found a mean utilization of 41.7 per cent of the dose given for 6 cases with iron deficiency anemia again examined with Fe^{59} labelled iron sorbitol

The present results should be compared with these figures The six hematologically normal controls had an average utilization of 26.4 per cent of the Fe^{59} dose and thus deviate inconsiderably from the normal values quoted above

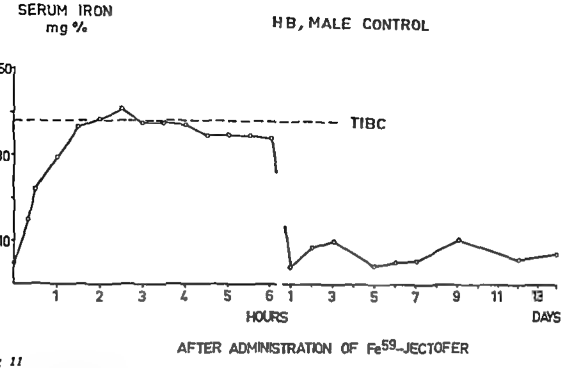


Fig 11
Serum iron concentration during the test period The transferrin concentration at the beginning of the trial is indicated
Male control subject

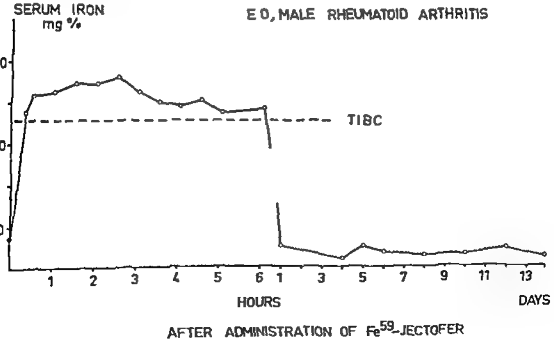


Fig 12
Serum iron concentration during the test period The serum transferrin concentration at the beginning of the trial is indicated
Man with rheumatoid arthritis

The figures quoted above for utilization in iron deficiency cases are clearly higher than those found in the present study for both controls and patients with rheumatoid arthritis The large difference between the present arthritic cases and the iron deficiency materials can be said to indicate that there was no real iron deficiency in the arthritic patients and this is confirmed by the demonstration of storage iron in nearly all these cases

It has been said that the anemia of infectious states (and rheumatoid arthritis) is accompanied by a block between the reticuloendothelial cells and the precursors of erythrocytes preventing reutilization of iron from decomposing erythrocytes and hence leading to hypoferremia (13 14) If this block functioned in the arthritic patients and the iron from the injected preparation passed only via the reticuloendothelial system the utilization of the labelled preparation should have been reduced or delayed in these patients compared with the controls This does not appear to have been the case the utilization being pretty well normal in the arthritic group compared with the controls It seems from this part of the study that the radioiron from Fe^{59} iron sorbitol is largely incorporated directly in marrow receptors (=erythrocyte precursors) and thus shunted past the reticuloendothelial system and the block

Previous investigations have shown that the transferrin bound iron in patients with rheumatoid arthritis is utilized to a normal degree (14 32 45 47) Only approx 6 per cent of the iron in iron sorbitol was liberated *in vitro* in plasma and bound to the transferrin (24) and thus is of little account in the total metabolism of iron sorbitol Since the reticulocyte count is not greatly increased in patients with rheumatoid arthritis (30 18 47) the incorporation of plasma iron in immature red blood cells as demonstrated by Jandl and co workers (17) and Najean (28 29) is probably not very important either

The slight fall in the erythrocyte indexes MCH and MCHC found in the arthritic patients in this material (Table I) and previously reported (14 19 30) indicates that there is a certain iron deficiency as a result of defective hemoglobinisation of the circulating erythrocytes In the present material of patients with rheumatoid arthritis and in a material published elsewhere (47) the great majority of patients had demonstrable storage iron but even so MCH and MCHC were somewhat low possibly because of the block already mentioned between the reticuloendothelial cells and the precursors of the erythrocytes This study has shown that in spite of the presence of storage iron in these patients there was good utilization in circulating erythrocytes of the Fe^{59} labelled iron sorbitol administered A further investigation has been planned to determine whether these patients display a normalization of MCH and MCHC and an increase in total hemoglobin when iron sorbitol is given in the adequate dose

The fact that no correlations were found between the different hematological variables and the utilization of Fe^{59} labelled iron sorbitol may be due to the limited size of the material as well as to the large scatter of the variables in individuals and groups (cf 50)

b Distribution of Fe^{59} iron sorbitol between different organs

The external measurements show that there was no considerable storage of Fe^{59}

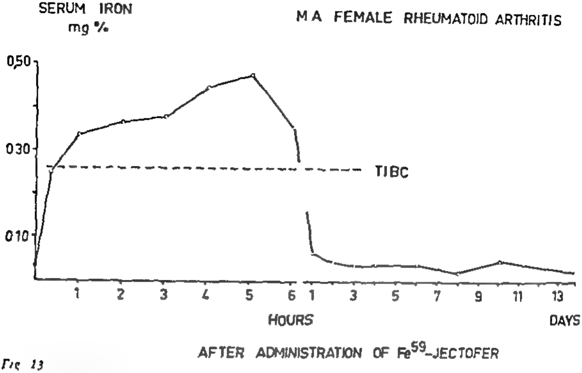


Fig 13

Serum i on concentrat on dur ng the test per od The serum transferr n concentrat on at the beginning of the trial is ind cated

Woman v th rheumatoid arthr t s

Table III

DISTRIBUTION OF LABELLED JECTOFER

	Controls				Rh umato d arthr t s				Iron defic ency
	n	Me n	$\pm_\varepsilon M$	S D	n	Mean	$\pm_\varepsilon M$	S D	
Per cent of njected dose ut l zation in red cells after 14 days	6	6 4	9		11	28 4	4	8 0	3 5
Per cent of injected dose excreted in ur ne	6	9 6	5 3	14 7	10	33 5	5 0	15 (	1 0
Per cent of n ected dose at nject on s te after 14 days	6		0	0 5	11	4 5	0 6	1	3
Per cent of injected dose unaccounted after 14 days	6	41 4	8	1 5	10*	3 9	3 5	11 0	39 5

* In one patient w th rl eumatoid arthr t s tl e f rst day s m ne spec men as lost

There was nothing to show that there had been any increased incorporation of the labelled preparation in the spleen in patients with rheumatoid arthritis compared with the controls

The incorporation curves over the liver showed a slower course compared with bone marrow with the maximum during days 3—9 followed by a falling course indicating elimination from the organ No difference was found between the groups though one patient with rheumatoid arthritis and signs of ineffective erythropoiesis showed high activity over liver and spleen

External measurements over bone marrow showed a rapid incorporation and elimination in good agreement with incorporation in circulating erythrocytes

Urinary excretion of the dose of Fe^{59} iron sorbitol amounted to a mean of 33 5 per cent for 10 of the patients with rheumatoid arthritis 29 6 per cent for the control group and 21 7 per cent the lowest value for the iron deficiency patient

Analysis of correlations was made for the utilization of Fe^{59} labelled Jectofer by erythrocytes as a function of different hematological variables with negative results

The reasons are discussed for believing that iron from this low molecular iron sorbitol complex can be utilized directly by precursors of erythrocytes without first being metabolized in the reticuloendothelial system

Acknowledgement

The author is grateful to Dr Stig Wahlqvist of AB Astra Södertalje for providing labelled Jectofer and to AB Astra for financial support

in the spleen which agrees with observations by Wohler (56) In this respect iron sorbitol differs from the high molecular preparations, as pointed out by Wohler (56) and Fielding (12)

The increase of the specific activity over the liver, at a slower rate compared with the curve over bone marrow, suggests that part of the Fe^{59} iron sorbitol is metabolised via the reticuloendothelial system There was no significant difference between normals and arthritic patients but one case (Fig 7), with signs of ineffective erythropoiesis displayed high activity over liver and spleen as well as a low percentage incorporation in circulating erythrocytes (by 14 per cent) In this patient the greater part of the preparation administered was stored in depot organs where it even remained for the next 3 weeks during a period of desferrioxamine treatment During an observation period of 3 5 years this patient had been persistently refractory to all iron therapy after transfusions her hemoglobin concentration has adjusted to 7—9 g/100 ml and she has persistently displayed hypoferremia During corticosteroid therapy the hemoglobin concentration rose to 12 g/100 ml and the serum iron concentration also displayed a rising tendency even though no iron was administered A mobilisation and a better utilization of storage iron can be demonstrated in arthritic patients during corticosteroid therapy (45) This corticosteroid effect will be dealt with in a subsequent paper (Chapter VII)

Thus in patients with anemia characterized by ineffective erythropoiesis even the low molecular iron sorbitol complex is largely stored in the reticuloendothelial system where it is of no benefit to the erythropoiesis (cf 16)

c Serum iron concentration

The serum iron concentration returned to the initial level after 24 hours in all cases with rheumatoid arthritis and in the patient with iron deficiency, this is perhaps natural since only one dose was given during the experiment In 2 normal cases there was a somewhat slower return to initial values i e 2 and 3 days after the injection of the test dose The other four controls displayed the same rapid return to initial values as the patients with rheumatoid arthritis

Summary

Eleven patients with rheumatoid arthritis 6 normal controls and 1 patient with iron deficiency anemia have been studied in respect of the utilization in circulating erythrocytes the urinary secretion and the distribution between liver spleen and bone marrow of Fe^{59} labelled iron sorbitol citric acid (Jectofer)

The mean utilization in circulating erythrocytes after 14 days in the group with rheumatoid arthritis was 28 4 per cent of the dose of Fe^{59} Jectofer in the control group 26 4 per cent and in the patient with iron deficiency 37 5 per cent The utilization in the group with rheumatoid arthritis was thus not lower than in the control group though it was lower than in previously published materials of iron deficiency patients as well as the present case of iron deficiency

The elimination from the injection site was rapid and almost complete in all subjects after 14 days 4 5 per cent of the test dose remained in the arthritic group and 2 7 per cent in the controls while the iron deficiency patient had 2 per cent after 10 days

There was nothing to show that there had been any increased incorporation of the labelled preparation in the spleen in patients with rheumatoid arthritis compared with the controls

The incorporation curves over the liver showed a slower course compared with bone marrow with the maximum during days 3—9 followed by a falling course indicating elimination from the organ No difference was found between the groups though one patient with rheumatoid arthritis and signs of ineffective erythropoiesis showed high activity over liver and spleen

External measurements over bone marrow showed a rapid incorporation and elimination in good agreement with incorporation in circulating erythrocytes

Urinary excretion of the dose of Fe^{59} iron sorbitol amounted to a mean of 33 5 per cent for 10 of the patients with rheumatoid arthritis 29 6 per cent for the control group and 21 7 per cent the lowest value for the iron deficiency patient

Analysis of correlations was made for the utilization of Fe^{59} labelled Jectofer by erythrocytes as a function of different hematological variables with negative results

The reasons are discussed for believing that iron from this low molecular iron sorbitol complex can be utilized directly by precursors of erythrocytes without first being metabolized in the reticuloendothelial system

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CHAPTER IV

BLOOD PLASMA AND RED CELL VOLUMES IN PATIENTS WITH RHEUMATOID ARTHRITIS OR IRON DEFICIENCY AND IN CONTROLS

by *O Strandberg*

Introduction

One of the factors which has been discussed as a possible cause of anemia in patients with active rheumatoid arthritis is dilution of the blood as a result of an increased plasma volume The literature up to 1962 in this field has been summarized and discussed by Read & co-workers (23)

The methods used have been plasma volume estimations with Evans Blue (9 13 16 17 22) or bromsulphalein (24) or isotope techniques with transferrin bound Fe^{59} (9 32) or Cr^{51} (22 23 32) Read & al (23) also used I^{131} tagged albumin

This paper concerns the determination of total hemoglobin blood volume plasma volume and red cell volume in patients with rheumatoid arthritis compared with patients with true iron deficiency and healthy controls The results did not indicate hemodilution from a plasma volume increase in the arthritic subjects the anemia being produced by reduction of the hemoglobin concentration total hemoglobin and red cell volume

Material

The majority of the patients and controls have been described in detail in Chapter II

a Patients with rheumatoid arthritis

Fourty five women and 16 men with active rheumatoid arthritis all of whom met the diagnostic criteria of the American Rheumatism Association (1 2)

b Patients with iron deficiency

Seven women and 5 men in accordance with the diagnostic criteria of Bothwell & Finch (4) and Bainton & Finch (3) The entire group is described in Chapter II

c Controls

Twenty seven women and 11 men apparently healthy and with normal hematological findings The selection of the subjects has been described in Chapter II

Laboratory methods

a The hemoglobin concentration was determined in venous blood as alkaline oxyhemoglobin and read at 540 mm The mean of 3—5 determinations on each subject was used

b The total hemoglobin (THb) was determined by the alveolar CO method of Sjöstrand (26 27) with modifications by Linderholm & Sjostrand (20) Wiklander (33) Linderholm & Soderstrom (19) Strandell (31) Duplicate determinations were made with an interval of one or two days except in 3 controls and 3 patients with rheumatoid arthritis in whom only one determination was made

c The blood volume (BV) was calculated from values obtained for THb and hemo

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of the old values and were more in keeping with blood volumes obtained with isotope dilution techniques (14, Ekelund, pers. comm.). Accordingly the values in this investigation obtained before April 1962 have been corrected by a factor of 0.918.

All laboratory work with the subjects was done at the same time of day. The venous blood for Hb determination was drawn in the morning. The THB and blood volume determinations were performed at about 11 a.m.

The in-patients (rheumatoid arthritis, iron deficiency) were lying in their beds and the controls were up and about at the time of the THb and blood volume determinations (cf. Discussion).

Results

The means, standard deviations and ranges of the anthropometric data, hemoglobin concentration, total hemoglobin as well as blood, plasma and red cell volumes for the six groups studied are given in Table II.

Table III gives the differences between the largest groups and Table IV the percentage differences between the patient groups and their respective control groups. A statistical analysis with the calculation of the significance of the differences between the means has been made in the largest groups only, i.e. the female and male patients with rheumatoid arthritis and their control groups.

a. Age. The mean ages of the arthritic and iron deficient groups are fully comparable; the control groups have a lower mean (Table II:1). It was not possible to select the subjects according to age.

b. Body build (Tables II:2—4, III, IV). The mean body weight is lower for the rheumatoid subjects than for their controls: —4.2 kg = —6.7 per cent (not significant) for the females and —10.7 kg = —14.1 per cent (x) for the males. The female arthritic subjects had a highly significantly (xxx) lower mean weight than the male. The mean body height for the arthritic groups did not differ from their respective control groups. The iron deficient subjects did not differ from the controls in body build.

c. Hemoglobin concentration (Table II:5, III, IV).

The mean for the male control group was 13.7 g/100 ml, which is of the same magnitude as the figures given by Strandell (31). He found a mean of 13.3 g/100 ml, S.D. 0.92 g/100 ml in 74 healthy men aged 30—83 years using the same hemoglobinometry method as in this study.

The female and male patients with rheumatoid arthritis had much the same decrease in Hb concentration: —2.2 g/100 ml = —17.0 per cent (xxx) and —2.3 g/100 ml = —16.8 per cent (xxx) respectively. The *iron deficient subjects had a still lower Hb* concentration mean compared with the controls: 8.9 g/100 ml = —31.8 per cent and 11.1 g/100 ml = —19.0 per cent, respectively.

d. Total hemoglobin (Tables II:6—9, III, IV).

The means showed significant decreases for arthritic women (xxx) and men (xx) in comparison with their respective control groups: women —64 g = —13.1 per cent, men —148 g = —20.4 per cent. The significance of the differences was unaltered when related to body area and height. THb related to weight displayed non-significant differences for the same comparison, which

Table I

Method errors for the total hemoglobin and blood volume calculated from duplicate determinations Non smoking subjects 11 healthy women and 28 women with rheumatoid arthritis The determinations were made [redacted] intervals of 1—2 days

	Number of duplicate determinations	Range	Mean	Error of method $\pm \sqrt{\frac{\Sigma d}{2\ n}}$	Coefficient of variation % of mean
Total hemoglobin g Contr	11	437—642	520	19 9	3 8
Total hemoglobin g R A	28	311—655	464	18 7	4 0
Blood volume 1 Contr	11	*3 5—5 3*	*4 41*	*0 18*	*4 2*
Blood volume 1 R A	28	3 2—5 7	4 50	0 23	5 0

globin concentration of finger blood disregarding the slight underestimation arising from the assumption of a constant hemoglobin concentration in the total blood volume

$$BV = \frac{THb}{Hb\ conc}$$

The errors of method are given in Table I

d The plasma volume (PV) was calculated from the blood volume and hematocrit with a correction for trapped plasma (5) of 1 7 per cent when the samples were centrifuged for 5 minutes and 1 3 per cent when they were centrifuged for 10 minutes according to Garby & Vuille (12) An International High speed micro hematocrit centrifuge was used for the determination of the packed cell volume of peripheral (venous) blood A correction for total body hematocrit/venous hematocrit by a factor of 0 91 according to Chaplin & al (6) was used for the calculation of the plasma volume (cf Discussion) The plasma volume was calculated as

$$BV - RCV$$

(see below)

e The red cell volume (RCV) was calculated from the blood volume

$$RCV = BV \times Hct \times 0\ 91 \times 0\ 987$$

(0 987 is the correction term for trapped plasma)

f Statistical methods Conventional statistical methods were used (30)

The complete formula for the calculation of THb according to Linderholm & Sjostrand (20) was replaced by an approximate formula introduced by Linderholm and later modified and discussed by Strandell (31) A recent discussion of the alveolar CO method is given by Ekelund (7)

During this study in April 1962 the concentration of the CO calibrating gas was changed The means of THb and blood volumes for normal persons with the new calibrating gas amounted to 91 8 per cent

Table II continued

Variable	Mean	SD	Range
9 THblm g			
RA F	60	36 4	168—358
RA M	330	69 3	235—4 5
ID F	234	6 7	134—34
ID M	367	85	2 6—50
Contr F	96	3	4—363
Contr M	406	36 5	34 —4 2
10 Blo d volume 1			
RA F	4 16	0 35	3 1—5 6
RA M	5 38	0 9	3 8—6 6
ID F	4 58	0 41	4 0—5 1
ID M	5 80	0 6	5 0—6 8
Contr F	4 1	0 43	3 —5 1
Contr M	5 65	0 40	5 1—6
11 Bl d volun elkg n l			
RA F		17 8	49 4—104 6
RA M	83 9	14 1	64 6—105 4
ID F	74	7 5	63 5 83 0
ID M	8 0	1 6	60 1—103 5
Contr F	66 3	9 3	47 6— 8 4
Contr M	5 6	10	58 — 93 9
1 Bl d lu elm l			
RA F	56	0 30	09—3
RA M	3 06	0 40	9—3 69
ID F	5	0 1	59— 96
ID M	3 1	0 43	44—3 49
Contr	35	0 3	1 90— 94
Cont M	94	0 4	67—3 41
13 B d lun eln l			
RA F	5	0 31	1 85—3 4
RA M	3 08	0 49	—3 1
ID F	9	1 18	51— 99
ID	3 0	0 34	74—3 35
C nt F	51	0	0 —3 06
Cont M	3 1	0 19	93—3 50

Variable	Mean	SD	Range
14 Plasma volume 1			
RA F	83	0 58	2 18—3 5
RA M	3 50	0 64	1 98—4 76
ID F	3 1	0 3	2 0—3 66
ID M	3 5	0 88	2 0—4.86
Contr F	2 63	0 9	04—3 18
Contr M	3 31	0 6	2 99—3 94
15 Plasma volumelkg ml			
RA F	49 2	9 0	33 0— 9
RA M	54 8	10 9	34 9— 0 6
ID F	52 2	8 5	0 3—66 6
ID M	5 4	13 4	3 1—65 8
Contr F	4	6 0	9 0—5 0
Contr M	44 2	6 4	34 4—54 1
16 Plas ma volu nelm l			
RA F	1 5	0 1	1 38— 34
RA M	1 97	0 32	1 3— 38
ID F	1 93	0 19	1 63— 17
ID M	1 88	0 45	1 30— 36
Contr F	1 55	0 19	1 06—1.88
Contr M	1 72	0 14	1 50—1 96
17 Plasma lun eln l			
RA F	1 74	0 1	1 9— 18
RA M	2 00	0 33	1 1— 36
ID F	1 96	0 19	1 69— 6
ID M	1 94	0 45	1 47— 54
Contr F	1 60	0 16	1 3 —1 90
Contr M	1 85	0 10	1 3— 0
18 Red cell volume l			
RA F	1 34	0 1	0 9—1 9
RA M	1.88	0 48	1 1—3 0
ID F	1 35	0 5	0 9— 0
ID M	2 9	0 31	1 9—
Contr F	1 51	0 18	1 —1 9
Contr., M	35	0 3	1 9—3 0

Table II

Anthropometr c data hemoglob n concentrat on total hemoglob n blood volume plasma olum and red cell volume absolute values and related to body parameters

Rheumatoid arthr t s females (n = 45) (R A F)
Rhemato d arthr t s males (n = 1() (R A M)
Iron deficiency females (n = 7) (*I D F*)
Iron deficiency males (n = 5) (I D M)
Controls females (n = 27) (Contr F)
Controls m ales (n = 11) (Contr M)

Variable	Mean	S D	Range
1 Age ye rs			
R A F	50 1	13 9	15—69
R A M	49 3	11 7	27—65
I D F	38 7	9 7	23—50
I D M	45 0	14 5	30—67
Contr F	37 1	15 6	17—67
Contr M	37 7	11 9	22—71
2 Body he ght cm			
R A F	162 8	5 4	153—173
R A M	174 1	7 1	164—187
I D F	163 7	8 0	154—177
I D M	181 2	7 6	172—181
Contr F	164 5	5 4	153—180
Contr M	178 3	5 8	170—189
3 Body weight kg			
R A F	58 9	10 5	40 6—83 5
R A M	65 1	13 1	48 0—99 0
I D F	62 3	11 6	48 6— 95
I D M	68 4	12 2	55 0—84 0
Contr F	63 1	8 4	49 0—85 0
Contr M	75 8	9 0	64 0—8 3
4 Body area m			
R A F	1 63	0 14	1 34—1 93
R A M	1 78	0 19	1 55 ?
I D F	1 67	0 18	1 44 1 96
I D M	1 87	0 19	1 67— 07
Contr F	1 69	0 10	1 51—1 94
Contr M	1 93	0 10	1 78—2 06

Variable	Mean	S D	Range
5 Hemoglob conc g/100 ml			
R A F	10 7	1 0	8 4—13 0
R A M	11 4	1 4	6 3—13 4
I D F	8 9	2 1	5 9—11 9
I D M	11 1	2 3	8 8—14 5
Contr F	12 9	0 8	11 4—14 7
Contr M	13 7	0 9	11 4—15 1
6 Total hem o glob n g			
R A F	423	64 2	285—590
R A M	577	136 6	404—845
I D F	386	118 6	20—60(
I D M	662	131 5	5 8—872
Contr F	487	61 0	386—610
Contr M	7 5	4 2	610—854
7 THb/kg g			
R A F	7 30	1 19	5 39—11 59
R A M	8 89	1 35	7 1C—11 80
I D F	6 15	1 1	4 4 — 7 6
I D M	9 99	2 94	6 7 14 51
Contr F	8	1 24	5 54—10 40
Contr M	9 67	1 39	11 1 03
8 THb/ g			
R A F	260	32 8	191 363
R A M	3 2	54 0	54—44
I D F	8	51 4	198 309
I D M	358	9 9	56—510
Cont F	89	33 0	30—349
Con r M	376	37 0	3 5 419

Table II continued

Variable	Mean	SD	Range
9 THblm g			
RA F	[illegible]60	36 4	168—358
R.A., M	330	69 3	235—[illegible]75
ID F	[illegible]34	6[illegible] 7	134—342
ID M	367	85 2	276—506
Contr F	296	3[illegible] 2	[illegible]4[illegible]—363
Contr M	406	36 5	34[illegible]—[illegible]
10 Blood volume l			
RA F	4 16	0 55	3 1—5 6
RA M	5 38	0 97	3 8—6 6
ID F	4 58	0 41	4 0—5 1
ID M	5 80	0 67	5 0—6 8
Contr F	4 1	0 43	3 [illegible]—5 1
Contr M	5 65	0 40	5 1—6 2
11 Blood volumelkg ml			
RA F	[illegible]	1[illegible] 8	49 4—104 6
RA M	83 9	14 1	64 6—10[illegible] 4
ID F	[illegible]4 2	[illegible] 5	63 5— 83 0
ID M	87 0	17 [illegible]	60 1—103 5
Contr F	66 3	9 3	47 6— 8[illegible] 4
Contr M	[illegible]5 6	10 [illegible]	58 [illegible]— 93 9
1[illegible] Blood volumelm l			
RA F	[illegible]5[illegible]	0 30	[illegible] 09—3 [illegible]7
RA M	3 06	0 40	[illegible] 49—3 69
ID F	[illegible]5	0 1[illegible]	[illegible] 58—[illegible] 9[illegible]
ID M	3 1	0 43	[illegible]44—3 49
Contr F	[illegible] 45	0 [illegible]3	1 96—[illegible] 94
Contr M	[illegible]94	0 [illegible]4	[illegible]67—3 41
13 Blood volumelm l			
RA F	[illegible]56	0 31	1 85—3 [illegible]4
RA M	3 08	0 49	2 [illegible]—3 [illegible]1
ID F	[illegible]9	0 19	[illegible]51—[illegible]99
ID M	3 [illegible]0	0 34	[illegible]4—3 55
Contr F	[illegible]51	0 [illegible]	0[illegible]—3 06
Contr M	3 1	0 19	[illegible]83—3 50
14 Plasma volume l			
RA F	2 83	0 [illegible]8	2 18—3 [illegible]5
RA M	3 50	0 64	1 95—4 [illegible]6
ID F	3 21	0 32	2 60—3 66
ID M	3 52	0 88	2 [illegible]—4 8[illegible]
Contr., F	2 63	0.29	2 04—3 18
Contr., M	3 31	0 [illegible]6	2 99—3 94
15 Plasma volumelkg ml			
RA F	49 2	9 0	33 0—[illegible]2 8
RA M	54 8	10 9	34 9—[illegible]0 6
ID F	5[illegible] 2	8 5	[illegible]0 3—66 6
ID M	52 4	13 4	3[illegible] 1—65 8
Contr F	42 2	6 0	29 0—52 0
Contr M	44 2	6 4	34 4—54 1
16 Plasma volumelm l			
R.A., F	1 75	0 21	1 38—[illegible] 34
RA M	1 97	0 32	1 23—2 38
ID F	1 93	0 19	1 63—2 17
ID M	1 89	0 45	1 30—2 36
Contr F	1 55	0 19	1 06—1.88
Contr M	1 72	0 14	1 50—1 96
17 Plasma volumelm l			
R.A., F	1 74	0 21	1 29—2 18
RA M	2 00	0 33	1 [illegible]1—[illegible] 36
ID F	1 96	0 19	1 69—2 26
ID M	1 94	0 45	1 47—[illegible] 54
Contr F	1 60	0 16	1 5[illegible] —1 90
Contr M	1 85	0 10	1 [illegible]5—[illegible] 02
18 Red cell volume l			
RA F	1 34	0 21	0 9—1 9
RA M	1 89	0 48	1 1—3 0
ID F	1 35	0 32	0 9—2 0
ID M	2 29	0 31	1 9—2 7
Contr., F	1 51	0 18	1 2—1 9
Contr., M	[illegible]35	0 3[illegible]	1 9—3 0

Table II, continued

Variable	Mean	SD	Range
19 Red cell volume/kg ml			
R.A F	23 1	4 4	16 4—33 0
R A M	29 0	6 0	22 4—41 3
I D F	21 8	4 3	16 4—27 7
I D M	34 6	9 4	24 9—48 9
Contr F	24 0	3 8	17 8—31 9
Contr M	31 4	5 8	22 8—42 7
20 Red cell volume/m l			
R A F	0 82	0 12	0 62—1 09
R A M	1 05	0 22	0 72—1 56
I D F	0 81	0 16	0 55—0 95
I D M	1 24	0 25	0 94—1 61
Contr F	0 89	0 10	0 71—1 10
Contr M	1 22	0 18	0 98—1 60
21 Red cell volume/m l			
R A F	0 82	0 12	0 54—1 09
R A M	1 09	0 26	0 65—1 66
I D F	0 82	0 18	0 50—1 05
I D M	1 27	0 19	1 01—1 54
Contr F	0 91	0 09	0 75—1 15
Contr M	1 32	0 17	1 04—1 67

is easily explained by the reduced mean weights in the arthritic groups (see above b)

There was a significant (xxx) difference between the sexes in *both arthritic and* control subjects (Table III c d) even when the THb was related to the body parameters

In the iron deficient subjects the mean THb was about 20 per cent lower for the women compared with the controls The iron deficent men showed a *moderate* decrease in THb (Table IV c, d)

The mean THb for healthy men in this series is 725, S D 74 g, which is no significantly different from the mean of 785, S D 118 g found by Strandell (31) in 74 healthy men

e Blood volume (Tables II 10—13 III IV) This study did not show very great differences between the patients and the controls except for the iron deficient women who had about a 12 per cent increase in mean blood volume (Table IV c) There were sex differences in both healthy and arthritic subjects

The mean blood volume for the male controls in this series was 5 65 S D 0 40 l which is of the same order as Strandell s

f Plasma volume (Tables II 14—17 III IV) The female patients with rheumatoid *arthritis showed a moderate but probably* significant (x) elevation of the mean plasma volume +0 20 l = +7 6 per cent (Tables *III a, IV a) The differences between female* arthritic and control subjects are greater when related to body weight height or sur*face area as already mentioned however* the lower weights of the arthritic subjects must be born in mind

The tendency *for the male arthritic group* is the same as for the female (Tables III b IV b)

There were sex differences for controls and rheumatoid subjects (Table III c d)

Table IV c d shows that the female iron deficient subjects in particular had an elevated mean plasma volume with a > 20 per cent increase as compared with the female control group Thus in this patient group the anemia seems to depend on an appreciable dilution factor

g Red cell volume (Tables II 18—21 III

Table III

Significance of differences between the means for anthropometric data and blood plasma and red cell volumes for 45 women with rheumatoid arthritis and 27 healthy women and for 18 arthritic women which low clinical activity (Shetlar group II) and 27 with high clinical activity (Shetlar groups III and IV)

Variable	a Rheum Arthr Fem Contr Fem	b Rheum Arthr Male Contr Male	Contr Fem Contr Male	d Rheum Arthr Fem — Rheum Arthr Male	e Rheum Arthr (III+IV) —II Females
Body length, cm	—1 7	—4 2	—13 8***	—11 3***	—1 4
Body weight, kg	—4 ?	—10 7**	—12 7***	—6 2	—8 1**
Body area m	—0 06	—0 15*	—0 24***	—0 15**	—0 10*
Hemoglobin conc g/100 ml	—2 2***	—2 3***	—0 8*	—0 7*	—0 1
Total hemoglobin, g	—64***	—148**	—238***	—154***	—32
Total hemoglobin/kg g	—0 52	—0 78	—1 85***	—1 59***	+0 43
Total hemoglobin/m g	—79***	—54**	—87**	—67***	—5
Total hemoglobin/m g	—36***	—76**	—110***	—70***	—17
Blood volume l	+0 04	—0 7	—1 53***	—1 2_***	+0 05
Blood volume/kg ml	+5 9*	+8 3	—9 5*	—11 7**	+11 0**
Blood volume/m l	+0 11	+0 17	—0 49***	—0 50***	+0 19*
Blood volume/m l	+0 05	—0 03	—0 66***	—0 5_***	+0 06
Plasma volume l	+0 23*	+0 19	—0 68***	—0 67***	+0 04
Plasma volume/kg ml	+7 0***	+10 6	—2 0	—5 6*	+7 6**
Plasma olume m l	+0 70***	+0 25	—0 17*	—0 22**	+0 13*
Plasma volume m l	+0 14**	+0 15	—0 25***	—0 _6***	+0 05
Red cell volume l	—0 17***	—0 47**	—0 84***	—0 54***	+0 02
Red cell volume kg ml	—0 ?	—? 4	—?4* *	—5 9***	+3 4
Red cell volume m l	—0 07*	—0 1**	—0 33***	—0 _3***	+0 06
Red cell olume m l	—0 09**	—0 24*	—0 41***	—0 26***	+0 01

IV) The tendency was the same as for hemoglobin concentration and THb There was a significant decrease in the female (xxx) and male (xx) arthritic groups compared with the controls The tendency remained when the red cell volume was related to body area and height

There were significant (xxx) sex differences among the controls and arthritic subjects (Table III c d)

The reduction in the mean red-cell volume was more marked in the iron deficient women than in the corresponding male group (Table IV c d)

Table IV

Body parameters and hemoglobin concentration total hemoglobin (THb) blood volume (BV) plasma volume (PV) and red cell volume (RCV) absolute values and related to the body parameters The percentage differences between the means for the arthritic and iron deficient groups and their respective control groups The corresponding means are given in Table II

Variable	Percentage difference from controls			
	Rheumatoid arthritis		Iron deficiency	
	a Women	b Men	c Women	d Men
Height	—1 0	—2 4	—0 5	+1 6
Weight	—6 7	—14 1*	—1 3	—9 8
Body area	—3 6	—7 8*	—1 2	—3 1
Hemoglobin conc	—17 1***	—16 8***	—31 0	—19 0
THb	—13 1***	—20 4**	—20 7	—8 7
THb/kg	—6 6	—9 1	—21 4	+3 3
THb/m	—10 0***	—14 4**	—21 1	—4 8
THb/m	—12 2***	—18 0**	—20 9	—9 6
BV	+1 0	—4 8	+11 2	+2 7
BV/kg	+9 9*	+11 0	+12 7	+15 1
BV/m	+1 5	+4 1	+12 2	+6 1
BV/m	+2 0	—2 8	+11 2	+0 9
PV	+7 6*	+5 7	+22 1	+6 3
PV/kg	+16 6***	+24 0	+23 7	+18 6
PV/m	+12 9***	+14 5	+24 5	+9 3
PV/m	+9 8**	+8 1	+22 5	+4 9
RCV	—11 3***	—20 0**	— 10 6	—2 6
RCV/kg	—3 7	—7 6	—9 2	+10 2
RCV/m	—7 9*	—13 9*	—9 0	+1 6
RCV/m	—9 9**	—18 2*	—9 9	—3 8

b Influence of the clinical activity of the rheumatoid disease The 45 women with rheumatoid arthritis have been divided into groups according to the clinical activity of their disease The scheme of Shetlar & co workers (25) has been used for clinical activity — group I slight or none group II mild, group III moderate group IV severe activity There were 18 subjects belonging to group II here termed low clinical activity and 27 from groups III and IV here termed high clinical activity (cf Chapter I)

Table III a and Table V show the differences for the means of the variables just discussed in a low and a high clinical activity group of the female arthritic patients

Table V

Differences between means for body parameters hemoglobin concentration total hemoglobin (THb) blood volume (BV) plasma volume (PV) and red cell volumes (RCV) in 18 rheumatoid women with low clinical activity (Shetlar group II) and 27 rheumatoid women with high clinical activity (Shetlar groups III and IV)

Variable	Clinical activity	Mean	Difference
Height, cm	II III + IV	163.6 162.2	1.4
Weight kg	II III + IV	63.8 55.7	8.1**
Area m	II III + IV	1.69 1.59	0.10*
Hemoglobin conc g/100 ml	II III + IV	10.8 10.7	0.1
THb g	II III + IV	442 410	32
THb/kg g	II III + IV	7.04 7.47	0.43
THb/m g	II III + IV	263 258	5
THb/m g	II III + IV	270 253	17
BV l	II III + IV	4.13 4.18	0.05
BV/kg ml	II III + IV	65.6 76.6	11.0**
BV/m l	II III + IV	2.45 2.64	0.19*
BV m l	II III + IV	2.52 2.58	0.06
PV l	II III + IV	2.81 2.85	0.04
PV/kg ml	II III + IV	44.6 52.2	7.6**
PV m l	II III + IV	1.67 1.80	0.13*
PV m l	II III + IV	1.71 1.76	0.05
RCV l	II III + IV	1.34 1.36	0.02
RCV kg ml	II III + IV	21.1 24.5	3.4
RCV m l	II III + IV	0.79 0.85	0.06
RCV m l	II III + IV	0.81 0.82	0.01

6

Table VI

Arthritic women (R A n = 45) and control women (Contr n = 27) Correlation analysis of weigth versus total hemoglobin (THb) blood volume (BV)/kg plasma volume (PV)/kg red cell volume (RCV)/kg and total hemoglobin versus hemoglobin concentration blood volume/kg red cell volume/kg and hemoglobin concentration versus red cell volume/kg

Variables	Subjects	r	Equation of regression line	Sample standard error y estimated from x
a y = THb	R A	+0.55***	y = 3.34 x + 226	54.3
x = Weight	Contr	+0.18		
b y = BV/kg	R A	−0.70***	y = 122 − 0.845 x	9.3
x = Weight	Contr	−0.72***	y = 116.5 − 0.795 x	6.6
c y = PV/kg	R A	−0.69***	y = 83.8 − 0.588 x	6.6
x = Weight	Contr	−0.68***	y = 73 − 0.488 x	4.4
d y = RCV/kg	R A	−0.63***	y = 38.6 − 0.262 x	3.5
x = Weight	Contr	−0.66***	y = 42.9 − 0.299 x	2.9
e y = Hb conc	R A	+0.49***	y = 0.0076 x + 7.52	0.9
x = THb	Contr	+0.42*	y = 0.0057 x + 10.1	0.8
f y = RCV/kg	R A	+0.14		
x = Hb conc	Contr	+0.44*	y = 2.01 x − 1.78	3.4
g y = BV/kg	R A	+0.01		
x = THb	Contr	+0.57**	y = 0.097 x + 24.1	7.8
h y = RCV/kg	R A	+0.13		
x = THb	Contr	+0.54**	y = 0.034 x + 7.7	3.2
i y = BV	R A	+0.43**	y = 0.022 x + 2.84	0.50
x = Weight	Contr	+0.21	y = 0.011 x + 3.42	0.48
k y = PV	R A	+0.40**	y = 0.014 x + 1.98	0.36
x = Weight	Contr	+0.23	y = 0.008 x + 2.11	0.35
l y = RCV	R A	+0.38*	y = 0.008 x + 0.89	0.16
x = Weight	Contr	+0.19	y = 0.0[illegible]4 x + 1.26	0.17

In the patient group shown in Tables III e and V, the clinical activity of the disease exerts an influence on the following variables body weight (xx) and consequently body area (x) blood volume per kg (xx) and m² (x) and finally plasma volume per kg (xx) and sq m (x)

i Correlation analysis The intercorrelations

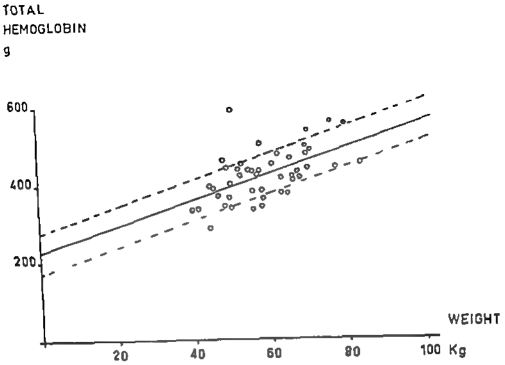


Fig 1
Total hemoglobin in relation to body weight in 45 women with rheumatoid arthritis
Regression line (Table VI a) ± 1 S D

between the body parameters and hemoglobin concentration total hemoglobin and blood volume have been extensively discussed by Strandell (31) in respect of healthy men Jeffrey (17) has made a correlation analysis of body weight and hemoglobin concentration versus blood plasma and red cell volumes in patients with rheumatoid arthritis and controls

In the present material an analysis of correlations between the variables examined has been made in the two largest groups arthritic and healthy women Table VI shows the correlations with their statistical significance

The total hemoglobin was significantly ($r = 0.55$***) correlated to body weight in the arthritic women (Fig 1 Table VI a) but not in the control group ($r = 0.18$)

With the body weight as an independent variable blood volume/kg plasma volume/kg and red cell volume/kg displayed significantly (xxx) negative correlations With increasing weight these variables tend to decrease at the same rate the slope of the regression lines does not differ much between the patients and the controls and the correlation coefficients are of the same magnitude (Table VI b—d)

The BV PV and RCV were positively

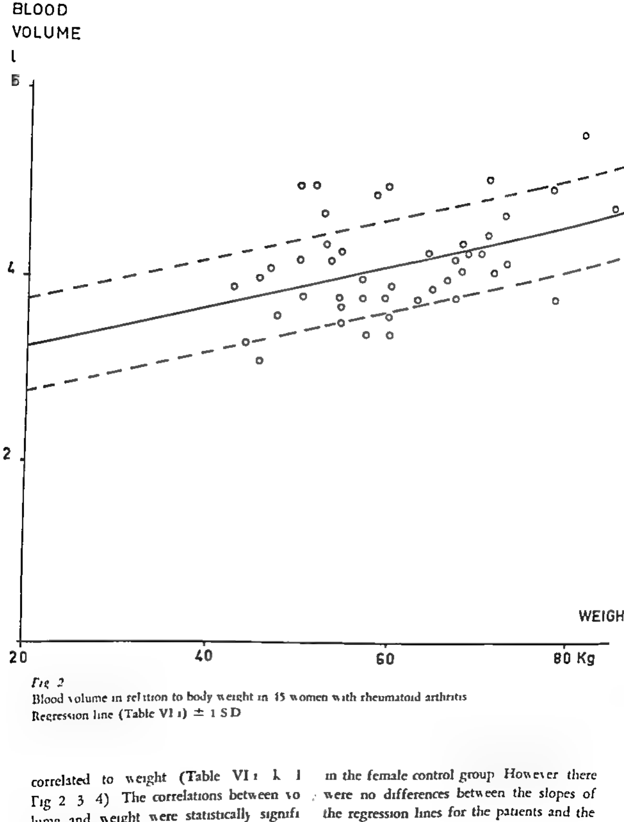


Fig 2
Blood volume in relation to body weight in 45 women with rheumatoid arthritis
Regression line (Table VI 1) ± 1 S D

correlated to weight (Table VI 1 k 1 Fig 2 3 4) The correlations between volume and weight were statistically significant in the arthritic female group, but not in the female control group However there were no differences between the slopes of the regression lines for the patients and the controls

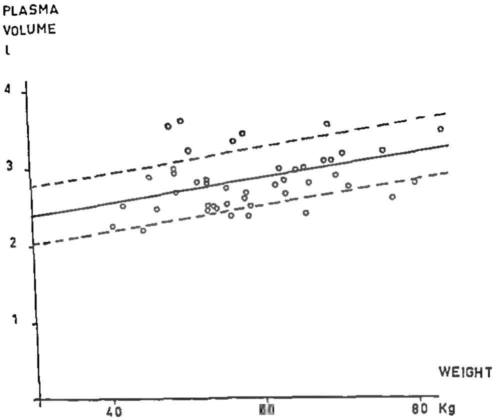
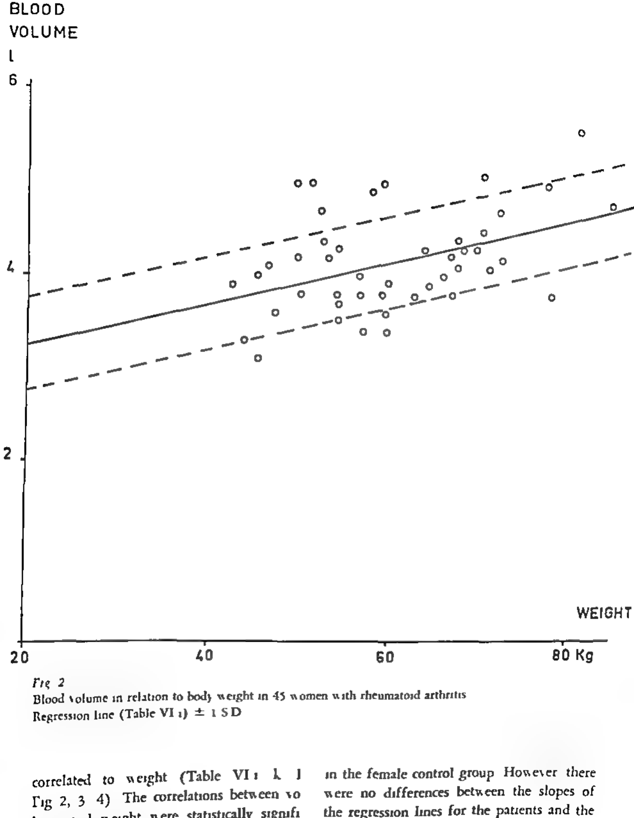


Fig. 3
Plasma volume in relation to body weight in 45 women with rheumatoid arthritis
Regression line (Table VI k) ± 1 S D

Discussion

The alveolar CO method for the determination of total Hb and blood volume has been discussed together with other methods by Sjostrand (29) Wiklander (33) Hallberg (15) Engstedt (8) Strandell (31) Ekelund (7) and others Wiklander (33) carefully compared the Evans Blue and P32 methods with the alveolar CO in hematologically normal surgical patients of both sexes He demonstrated a close correspondence between the total hemoglobin means in 38 subjects obtained with the CO method and P32 whereas the means for the same subjects were considerably higher with the Evans Blue method The figures for BV/kg BV/m² PV kg PV m² and RCV kg RCV m² in the present series for female and male controls are almost identical with the means obtained by Wiklander with the Evans Blue method and agree less well with his figures for the alveolar CO method

Ekelund (7) compared figures for THb blood and plasma volumes in 48 cases as



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ferrin method and 3.16 S.D. 0.87 with the albumin method. The differences between these means were not significant.

A comparison with Strandell's figures (31) for THb, BV and PV has been made in the preceeding section and showed a rather close correlation.

Sjöstrand (29) has tabulated the weight of blood corpuscles, expressed as a percentage of body weight, from the literature on different methods, including a large material in which the alveolar CO method was employed. The hemoglobin concentration in the red corpuscles was taken to be 35 per cent and their specific gravity 1.095. In 116 healthy males the average weight of blood corpuscles was 3.38 per cent of the body weight (present series 3.43 percent), and in 48 healthy females it was 2.63 per cent (present series: 2.66 per cent).

From the figures given it seems that the normal values obtained with the alveolar CO method in the present series lie well within the normal values for the laboratory. The good agreement with isotope dilution methods is also worth stressing, as most of the plasma volume determinations published recently have been performed with such methods.

Standards of reference

As shown in Tables II 3, III a, b and IV a, b the mean weights of the arthritic patients are lower than those of the controls. The difference is more marked in patients with a higher clinical activity of the disease (Tables III e, V). The interdependence of blood, plasma and red-cell volumes for healthy subjects has been discussed e.g. by Gibson & Evans (10) and Strandell (31) and for rheumatoid subjects by Jeffrey (16, 17). The blood volume in lightweight healthy subjects tends to be high in terms of weight, and low in heavyweight subjects. The same tendency is demonstrated for BV/kg, PV/kg and RCV/kg in both arthritic and healthy women in the present material (Table VI) in accordance with the findings of Jeffrey (17).

Sjöstrand (28) has demonstrated that there is no correlation between total hemoglobin and body height in adults. In the present material the patients with rheumatoid arthritis do not seem to have appreciably changed their body height (Tables II 2, III e, V). When evaluating and comparing the means obtained for the different groups of subjects, it seems worth relating the data to weight, body surface area and height. Relations to these three body parameters have therefore been made in the present material.

Total body hematocrit/venous hematocrit

No separate determinations of plasma volume or red cell volume were made in the present study. Instead, these values have been derived from the THb and blood volumes. The correction factor of 0.91 for total body hematocrit/venous hematocrit, according to Chaplin & al. (6) has been used.

Read & co-workers (23) measured the red-cell mass with radioactive chromium and the plasma volume with radioactive iodinated serum albumin (RISA) in 26 patients with rheumatoid arthritis and 40 controls. The means for body hematocrit/venous hematocrit were: for controls, males 0.909 (± 0.040), females 0.915 (± 0.045); and for arthritis patients, males 0.890 (± 0.023), females 0.870 (± 0.0315). The difference between these means was statistically significant in the female patient group but not in the male group. (The number of

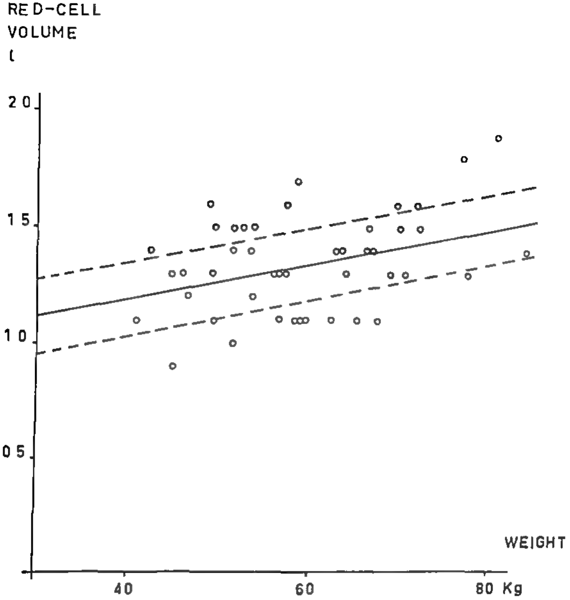

Fig 4
Red cell volume in relation to body weight in 45 women with rheumatoid arthritis
Regression line (Table VI 1) ± 1 S D

determined with the total hemoglobin (alveolar CO) method and the I^{131} albumin —10 minute space in whole blood measured with a volumetron (Williams & Fine 34) He found no significant difference between the two methods My own figures agree well with Ekelund s, in a following chapter (VI) the plasma volume was determined in a series of patients with rheumatoid arthritis and controls 10 persons using three different methods (1) alveolar CO (2) 10 minute space from transferrin — I^{131} or I^{125}, and (3) 10 minute space from albumin — I^{131} or I^{125} The means for the 10 subjects were 3 15, S D 0 52 with the CO method, 3 37 S D 0 79 with the trans

Applying Lange's (18) figure of an 8 per cent difference in plasma volume between the recumbent and the upright position the percentage difference between arthritic patients (recumbent before the blood volume determination) and controls (upright before the blood volume determination) is almost completely eliminated The difference between iron deficient females (recumbent) and controls still remains

Sex differences

The present study shows statistically significant differences between the means of the two sexes for total hemoglobin blood volume plasma volume and red cell volume in both arthritic and healthy subjects with lower means for women This difference has been demonstrated in healthy persons by Gibson & Evans (10) and others and in arthritic subjects by Jeffrey (16)

Summary

Fourty five women and 16 men with active rheumatoid arthritis 7 women and 5 men with iron deficiency and a control of 27 women and 11 men have been examined for hemoglobin concentration total hemoglobin (determined with the alveolar CO method) and from the total hemoglobin the blood plasma and red cell volumes were calculated

The hemoglobin concentration total hemoglobin and red cell volumes were highly significantly decreased in the arthritic patients compared with the controls The tendency was the same for these variables in the iron deficient groups

There was a moderate increase in the mean plasma volume in the arthritic patients compared with the controls +7 6 per cent for the females and +5 7 per cent for the males The difference can be explained by the effect of an upright position in the control subjects The increase in the mean plasma volume was more marked in the iron deficient patients +22 per cent for the female and +6 3 per cent for the male group

The mean blood volume was not different from normal values in the arthritic patients but elevated by 11 per cent in the iron deficient women

From this study the conclusion is drawn that the anemia in rheumatoid arthritis is a true anemia with reduction of hemoglobin concentration total hemoglobin and red cell volume hemodilution is not an important factor On the contrary the iron deficient women in this material showed signs of an appreciable hemodilution

subjects in the female and male groups was not indicated nor whether the red cell and plasma volume determinations were performed simultaneously.) As Lange (18) Ekelund (7) and others have pointed out the plasma and red cell volumes vary differently with time. The plasma volume alters quickly for example on changing from a recumbent to an upright position (8 per cent according to Lange). Thus the difference of 4 per cent between arthritic and healthy women in respect of total body hematocrit/venous hematocrit has not been considered large enough to be taken into account in the present material. Furthermore the patients with rheumatoid arthritis or iron deficiency were controlled with x-ray of the abdomen in order to exclude enlargement of the liver and spleen. There was no subject with pathological findings in this respect. This is of importance, as Loria & al (21) have demonstrated a significant deviation from the total body hematocrit/venous hematocrit figure of 0.91 in patients with a high degree of splenomegalia and in anemic subjects with a venous hematocrit < 25 per cent. There was no patient with such disturbances in the present series.

Results in patients with rheumatoid arthritis

Read & al (23) have summarized the findings of earlier studies and compared them with their own in rheumatoid arthritis patients. A decrease in the red cell mass was a consistent finding with significant differences in three out of five publications. An increase in plasma volume in arthritic patients was reported in three out of five publications. The blood volume was found to be increased by two observers and decreased by two.

In the present material of patients with rheumatoid arthritis the red cell volume was significantly decreased for both women and men, the plasma volume was slightly but significantly increased for the female group and non-significantly increased for the male group, compared with the control groups; the blood volume was slightly increased for the female group while the males showed no clear tendency (Table III).

Table IV shows that the percentage decrease of the hemoglobin concentration in the arthritic groups (females —17.1, males —16.8 per cent) is of the same magnitude as the decrease in total hemoglobin (females —13.1, males —20.4 per cent) and red cell volume (females —11.3, males —20.0 per cent).

The plasma volume increase is not of the same magnitude (females +7.6, males +5.7 per cent).

These figures thus strongly suggest that hemodilution is not a major factor behind the anemia in patients with rheumatoid arthritis. *This anemia is a true anemia with reduction of the hemoglobin concentration, total hemoglobin and red cell volume.*

Iron deficiency

In Chapter II considerable differences were reported for the peripheral blood picture, sternal marrow iron content and iron absorption pattern between arthritic and iron deficient patient groups. Table IV c-d shows that in the iron deficient patients the decrease in hemoglobin concentration was mostly the result of an increase in the plasma volume and to a lesser extent of a decrease in the red cell mass. The female group in particular displayed a considerable increase in blood and plasma volumes suggesting a more marked hemodilution in this group.

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Table 1

Errors of laboratory methods calculated from duplicate determinations
Samples from consecutive subjects

Laboratory method	Number of duplicate determinations	Range of values	Mean value	Method error $\pm\sqrt{\frac{\Sigma d}{2n}}$	Variation coefficient % of mean
Hemoglobin g/100 ml	[illegible]	1[illegible].2—13.8	13.09	0.34	2.6[illegible]
Serum iron µg/100 ml	40	[illegible]6—196	76.1	4.94	6.50
Packed cell volume per cent	21	31.0—47.8	38.[illegible]	1.76	4.61
Total hemoglobin g/100 ml	8	311—[illegible]55	4[illegible]	18.7	4.0
Total serum protein g/100 ml	14	[illegible].31—6.[illegible]8	6.63	0.29	4.35
Serum albumin, g/100 ml	15	3.07—3.9[illegible]	3.34	0.16	4.82
Serum alpha glob g/100 ml	15	0.81—1.04	0.90	0.06	6.19

Hemoglobin concentration from two different finger punctures different pipettes
Serum iron concentration determinations on the same samples on two subsequent days the second sample had a code number
Packed cell volume samples from two different venipunctures with 1—? days interval
Total hemoglobin determinations on two subsequent days
Total serum protein, albumin alpha globulin the same as for serum iron concentration

Laboratory methods

The blood samples from in patients were drawn in the morning when the patients were still in bed before the first morning meal The blood samples from the out patients were drawn when the patients were up and about but still fasting

Hemoglobin and serum iron concentration and packed cell volume were determined with standard methods as described in Chapter I and II

Total hemoglobin was determined by the alveolar carbon monoxide method according to Sjostrand (28) with some modifications (17 19 37) Duplicate determinations were made

The amounts of circulating albumin and total protein were calculated from the serum concentrations and the plasma volume derived from the blood volume and hematocrit determinations The blood volume was calculated from the values for total hemoglobin (29) and the hemoglobin concentration in finger blood When calculating the plasma volume correction was made for the difference between the hematocrit in venous blood and that of the total blood volume (body hematocrit = 0 91 × venous hematocrit) according to Chaplin & co workers (7)

Conventional statistical methods were used with calculation of mean values and standard deviations (30) Partial correlations were estimated according to Fisher (9)

The errors of laboratory methods are set out in Table 1

CHAPTER V

STUDIES IN ANEMIA AND PLASMA PROTEIN DISTURBANCES

by L Engstedt, S Johansson & O Strandberg

Introduction

Plasma protein disturbances in rheumatoid arthritis with low albumin and elevated alpha$_2$ globulin serum concentrations have been reported by many workers, summarized up to 1948 by Gutman (10)

Most of the publications have dealt with elevated protein fractions (alpha$_2$ globulin glycoproteins etc) and the correlations between these and the clinical activity of the rheumatic disease, see e g Shetlar & co workers (21 25 26, 27 31)

A connection between protein deficiency and anemia has been demonstrated and has been discussed by many workers (6 11, 14 15 20 35) However we have failed to find more than one publication (35) dealing with anemia in patients with rheumatoid arthritis as being possibly connected with nutritional deficiency or with disturbances in protein metabolism possibly causing defects in red cell and hemoglobin production

As a rule patients with active rheumatoid arthritis have anemia the serum albumin concentration is considerably decreased (10) and the weight is reduced (8 12)

With these facts in mind we have considered it worth while to study the possible relationship between anemia and protein deficiency in patients with rheumatoid arthritis A positive relation between serum albumin and hemoglobin concentrations was found, as well as between the total circulating amounts of albumin and hemoglobin Other serum protein components were studied in relation to hematological parameters and clinical activity

Material

1 One hundred and four female and 44 male in patients with definite and classical active rheumatoid arthritis according to the American Rheumatism Association (A R A 1, 2 3) and with clinical activity I—IV according to Shetlar & co workers (26) were studied with respect to hematological and serum protein values These patients have been presented in Chapter I

2 In order to determine whether the hemoglobin concentration is better correlated with the glycoproteins than with the serum proteins as evaluated by paper electrophoretic analysis a second group was studied Fourty five women with rheumatoid arthritis (1 2 3) 5 in patients and 40 out patients were analysed with respect to the concentrations of glycoproteins and haptoglobin in serum The analyses of these serum components were made by Bottiger Malmqvist & Olhagen (5) and have kindly been placed at our disposal

3 Fifty women and 11 men in patients with rheumatoid arthritis were studied in respect of total hemoglobin and serum proteins They were chosen according to the same criteria as the other patients in this study

Table III

43 women with rheumatoid arthritis Data from 5 in patients and 38 out patients Correlations between the hemoglobin concentration and serum protein fractions and glycoproteins clinical activity and rheumatoid factor (33) and haptoglobin The glycoprotein values and haptoglobin were kindly supplied by Bettiger Malmqvist & Olhagen (5)

Variable	n	Mean	r
Hb Total protein	43	7 24	—0 01
Hb Serum albumin	40	4 32	0 2‾
Hb Serum alpha$_1$ globulin	40	0 39	—0 27
Hb Serum alpha globulin	40	0 ‾9	—0 42**
Hb Serum beta globulin	40	0 66	0 10
Hb Serum gamma globulin	40	1 58	—0 21
Hb Serum hexose	43	145	—0 34*
Hb Serum hexosamin	43	119	—0 ,0***
Hb Serum sialic acid	43	81 4	—0 48**
Hb Serum total glycoproteins	43	346	—0 47**
Hb E S R	43	36 7	—0 61***
Hb Clinical activity[1]	43	2 4	—0 24
Hb Rheumatoid factor	43	7 9	—0 14
Hb Serum haptoglobin	39	?20	—0 16
Hemoglobin concentration	43	10 9	

[1] Clinical activity according Shetlar & al (26) Group I slight or none II mild III moderate, IV Severe activity

Rheumatoid factor arbitrary scale 1 3 — 5 1 64 = 6, 1 128 = ‾ [illegible] 1 32 768 = 15

vity and especially the glycoproteins as earlier shown by Shetlar & co workers (21 25 26 27 31)

Correlations between clinical activity and anemia

Table II (material 1) shows highly significant differences between low and high clinical activity in patients with rheumatoid arthritis in respect of the concentrations of hemoglobin and serum iron This finding has also been rather extensively discussed in Chapter I

It is common practice to relate the clinical activity of rheumatoid arthritis to the concentrations of glycoproteins in serum (see e g 21 25 26 27 31) From Table III it is clear that there are highly significant correlations in material 2 between the hemoglobin concentration on the one hand and the hexosamin concentration and ESR on the other significant correlations were found

Table II

Differences between mean values of hematological and serum protein data 104 women with rheumatoid arthritis Comparisons between low (Shetlar groups I and II) and high (groups III and IV, ref 26) clinical activity

Variable	Activity group	n	Mean	Difference
Hemoglobin	I + II III + IV	38 66	11 04 10 05	0 90***
Serum iron	I + II III + IV	38 66	85 62	23***
ESR	I + II III + IV	38 66	34 0 53 2	19 2***
Total protein	I + II III + IV	38 66	7 43 7 35	0 08
Albumin	I + II III + IV	38 66	4 04 3 74	0 30**
$Alpha_1$ globulin	I + II III + IV	38 66	0 43 0 45	0 02
Alpha globulin	I + II III + IV	38 66	0 75 0 89	0 14***
Beta globulin	I + II III + IV	38 66	0 65 0 66	0 0[illegible]
Gamma globulin	I + II III + IV	38 66	1 51 1 60	0 09
Rheumatoid factor[1]	I + II III + IV	38 66	5 74 7 59	1 85*
Weight	I + II III + IV	37 65	59 1 55 3	3 8

1 Rheumatoid factor (33) arbitrary scale 1 32 = 5 1 64 = 6 1 128 = 7 1 32768 15

Results

Correlation between clinical activity and elevated serum protein components

Table II shows results from material 1 with a highly significant difference between low and high clinical activity in respect of ESR and $alpha_2$ globulin concentration

In material 2 it has been demonstrated by Bottiger Malmqvist & Olhagen (5) that there is a relation between the clinical acti

Table IV

104 female in patients and 40 out patients with rheumatoid arthritis Differences in the concentration of serum protein and albumin

	n	Mean	S D	Error of the mean
Total protein, in patients	104	7 35	0 60	0 06
Total protein, out patients	40	7 74	0 49	0 08
Difference		0 39		
t		4 05		
P		<0 001		
Serum albumin in patients	104	3.85	0 52	0 05
Serum albumin out patients	40	4 32	0 46	0 07
Difference		0 46		
t		5 [illegible]1		
P		<0 001		

reduced by about 8 per cent according to Lange Table IV shows that there is a statistically highly significant difference in the serum concentrations of total protein and albumin between the 104 patients in bed (material 1) and the 40 out patients (material 2) The difference in total serum protein concentration is about 5 per cent and in albumin concentration about 11 per cent well in accordance with the figures of Lange

Table V shows that material 1 displays highly significant correlations between the concentrations of hemoglobin and serum albumin and also between the concentrations of serum iron and albumin No correlation is obtained between these variables and the total serum protein concentration

Table VI shows a complete partial correlation analysis according to Fisher (9) of the relevant parameters (cf Table V parameters significantly intercorrelated) After elimination of the variables according to the arrangement in Table VI significance remains between the concentrations of hemoglobin and albumin. The correlations between the concentrations of hemoglobin and serum albumin decrease when the variables serum iron and ESR are eliminated which is in accordance with the results mentioned above

The significance of differences between the correlation coefficients (before elimination) in the female and male groups has been tested after z transformation, according to Fisher (9) The results are indicated to the right in Table VI A highly significant *difference* was found between the r values of serum iron versus ESR and a probably significant difference between the female/

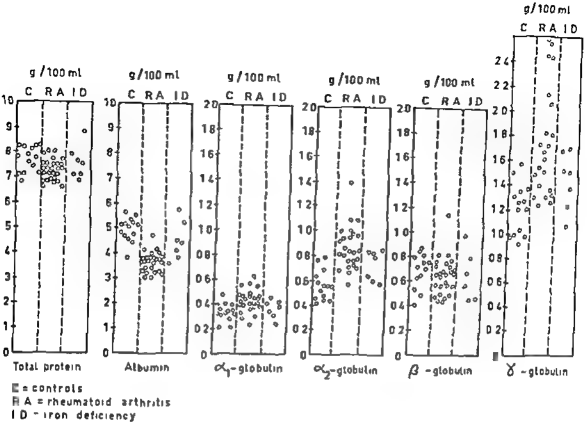

Fig 1

Total serum protein and paper electrophoretic fractions in 14 healthy women 27 women with rheumatoid arthritis and 7 women with uncomplicated iron deficiency
C = controls R A = rheumatoid arthritis I D = iron deficiency

between the hemoglobin concentration and alpha$_2$ globulin sialic acid and total glycoprotein concentrations

Correlations between anemia and deficit of serum protein components

Fig 1 shows that in patients with active rheumatoid arthritis there is a considerable decrease in the serum albumin concentration and also an increase in the serum alpha$_2$ and gamma globulins By way of comparison findings are given for 7 women with uncomplicated iron deficiency anemia and 14 healthy women The decrease in albumin concentration is not so marked in the iron deficiency group as in the arthritic group

Perera & Berliner (23) and Lange (16) have demonstrated that total serum protein values are significantly higher in ambulatory persons than in those resting in bed The reason is assumed to be hemodilution in the recumbent position resulting from a return into the circulation of edema fluid which collects in the legs on standing Thus the differences in the actual serum protein concentrations between patients with rheumatoid arthritis in bed and controls who are up and about (Fig 1) should be

male groups when serum iron and hemoglobin correlation coeffients were compared

All correlation coefficients have higher values in the male than in the female group (Table V VI) Elimination with these numerically larger coefficients in the male group will therefore give a lower remaining significance

Table VII shows that the total amounts of circulating hemoglobin and albumin in material 3 are highly significantly intercorrelated There is also a significant correlation between total hemoglobin and total circulating amount of protein ($P < 0.001$) One explanations for these correlations is that blood and plasma volumes increase with body weight (32) Consequently relations have been made to the body parameters weight and body area after which the correlations remain highly significant

Discussion

Many authors have found good correlations between clinical activity of the rheumatic disease and elevated concentrations of serum protein fractions such as alpha$_2$ globulin and glycoproteins (5 19 21 25 26 27 31) Correlations between the degree of anemia and clinical activity have also been demonstrated The clinical activity has been classified according to clinical methods of judging activity (12 13) and/or elevation of the E S R glycoproteins alpha$_2$ globulin concentrations (21 25 26 27 31) In material 2 a good relation was found between anemia as measured by the hemoglobin concentration and these last mentioned variables (see Table III)

Investigations on protein deficiency and hemoglobin synthesis have been published dealing with both animals and human subjects Orten & Orten (20) cited the literature back to the end of the 19th century They showed that the occurrence of low protein anemia in rats was not cured by alterations in calories minerals including iron or vitamins Whipple & al (36) could differentiate between iron and protein as limiting factors in hemoglobin synthesis working with the standard anemic dog Bethard & al (4) who worked with rats demonstrated that removal of protein from the diet was followed by blood volume diminution and reduction in erythropoiesis Shahidi & al (24) reviewed the literature and studied two babies 2—3 months old with cystic fibrosis of the pancreas who had hypoproteinemia hypoalbuminemia and anemia with decreased concentration of serum iron and transferrin as a result of the protein failure The anemia was normocytic and normochromic, the bone marrow showed decreased erythroid activity iron deficiency was considered to be unlikely Intake of high quality protein without extra iron gave response in reticulocytes hemoglobin concentration and transferrin values The protein deficiency was assumed to be a cause of the anemia The T ½ of I^{131} tagged albumin was within the normal range

Pearson & al (22) observed that in iron deficient rats the rise in hemoglobin concentration after institution of iron was significantly lower in protein deficient animals compared with those who had adequate protein intake

Hallgren (11) showed that the deleterious effect of protein deficiency upon hemoglobin synthesis was not related to the amount of iron stored in the marrow liver or spleen The hemoglobin synthesis was not privileged in relation to other needs in the competition for material for protein synthesis When the intake of iron was adequate low

Table V

Correlation coefficients between hematological and serum protein variables and ESR in 104 women and 44 men with rheumatoid arthritis (Material 1). ESR in mm/1 hour. Protein components and hemoglobin concentrations in g/100 ml, serum iron concenration in μ/100 ml

Variables	Women			Men		
	n	Mean	r	n	Mean	r
Albumin Hemoglobin	104	3.85 10.41	0.35***	44	3.76 11.29	0.51***
E.S.R. Hemoglobin	104	47.1 10.41	—0.29**	43	49.0 11.35	—0.41**
Total protein Hemoglobin	104	7.35 10.41	0.03	44	7.55 11.29	0.16
Serum iron Hemoglobin	104	70.4 10.41	0.29**	42	72.5 11.21	0.59***
Albumin Serum iron	104	3.85 70.4	0.39***	42	3.74 72.5	0.57***
E.S.R. Serum iron	104	47.1 70.4	—0.14	41	49.2 73.2	—0.69***
Total protein Serum iron	104	7.35 70.4	0.05	42	7.55 72.5	—0.07
Alpha$_2$ globulin Hemoglobin	104	0.84 10.41	—0.16	44	0.89 11.29	—0.38*
Alpha$_2$ globulin Serum iron	104	0.84 70.4	—0.24*	42	0.89 72.5	—0.53***

Table VI (continued)

SI Alb	0.386***	0.569***	No significance
SI Alb Hb	0.318**	0.388*	
SI Alb ESR	0.366***	0.346*	
SI Alb α	0.322***	0.379*	
SI Alb Hb ESR	0.319**	0.209	
SI Alb Hb α	0.389***	0.23[illegible]	
SI Alb ESR α	0.3[illegible]7***	0.[illegible]86	
SI Alb Hb ESR α	0.277**	0.165	
SI α	−0.236*	−0.531***	No significance
SI α Alb	−0.076	−0.301	
SI α Hb	−0.201*	−0.410**	
SI α ESR	−0.196*	−0.227	
SI α Alb ESR	−0.094	−0.103	
SI α Hb ESR	−0.196*	−0.159	
SI α Alb Hb	−0.077	−0.276	
SI α Alb Hb ESR	−0.107	−0.091	
SI ESR	−0.137	−0.688***	Significant P < 0.001
SI ESR Alb	0.034	−0.561***	
SI ESR Hb	−0.058	−0.604***	
SI ESR α	−0.079	−0.551***	
SI ESR Alb Hb	0.066	−0.534***	
SI ESR Alb α	0.065	−0.504**	
SI ESR Hb α	−0.010	−0.506***	
[illegible] ESR Alb Hb α	0.080	−0.483**	
ESR α	0.475***	0.576***	No significance
ESR α Alb	0.350***	0.398**	
ESR α SI	0.460***	0.343*	
ESR α Hb	0.454***	0.496***	
ESR α Alb SI	0.349***	0.[illegible]93	
ESR α Alb Hb	0.354***	0.384*	
ESR α SI Hb	0.455***	0.341*	
ESR α Alb SI Hb	0.368**	0.29[illegible]	
ESR Alb	−0.4[illegible]***	−0.531***	No significance
ESR Alb SI	−0.409***	−0.301	
ESR Alb Hb	−0.364[illegible]*	−0.410**	
ESR Alb α	−0.[illegible]**	−0.[illegible]27	
ESR Alb SI Hb	−0.365***	−0.103	
ESR Alb SI α	−0.2[illegible]**	−0.159	
ESR Alb Hb α	−0.[illegible]1[illegible]*	−0.[illegible]76	
ESR Alb SI Hb α	−0.[illegible]6*	−0.091	
Alb α	−0.419***	−0.578[illegible]**	No significance
Alb α SI	−0.399*	−0.396**	
Alb α Hb	−0.425***	−0.487**	
Alb α ESR	−0.137	−0.403**	
Alb α SI Hb	−0.3[illegible]***	−0.384*	
Alb α SI ESR	−0.071	−0.354*	
Alb α Hb ESR	−0.313[illegible]*	−0.363*	
Alb α SI Hb ESR	−0.[illegible]68**	−0.361	

Table VI

104 women and 44 men with rheumatoid arthritis. Partial correlations between the concentration of hemoglobin (Hb), serum iron (SI), albumin (Alb), alpha$_2$ globulin (α_2) and ESR. Significance of differences between the correlation coefficients for women and men after z transformation

Variables	Women r	Men r	Significance of difference between $r_{women} - r_{men}$ (before elimination)
Hb Alb	0.347***	0.510***	No significance
Hb Alb SI	0.263**	0.265	
Hb Alb ESR	0.259**	0.381*	
Hb Alb α_2	0.312**	0.384*	
Hb Alb SI ESR	0.180	0.267	
Hb Alb SI α_2	0.245*	0.245	
Hb Alb ESR α_2	0.264**	0.338*	
Hb Alb SI ESR α_2	0.195	0.248	
Hb SI	0.290**	0.587***	Significant 0.05 > P > 0.01
Hb SI Alb	0.180	0.420**	
Hb SI ESR	0.264**	0.457***	
Hb SI α_2	0.244*	0.491***	
Hb SI Alb ESR	0.189	0.375*	
Hb SI Alb α_2	0.180	0.405**	
Hb SI ESR α_2	0.264**	0.432**	
Hb SI Alb ESR α_2	0.195	0.371	
Hb α_2	—0.159	—0.381*	No significance
Hb α_2 Alb	—0.004	—0.123	
Hb α_2 SI	—0.097	—0.101	
Hb α_2 ESR	—0.026	—0.192	
Hb α_2 Alb SI	—0.010	—0.003	
Hb α_2 Alb ESR	—0.058	—0.005	
Hb α_2 Alb ESR	—0.028	—0.102	
Hb α_2 Alb SI ESR	—0.027	—0.008	
Hb ESR	—0.289**	—0.414**	No significance
Hb ESR Alb	—0.166	—0.206	
Hb ESR SI	—0.263**	—0.017	
Hb ESR α_2	—0.246*	—0.258	
Hb ESR Alb SI	—0.179	0.040	
Hb ESR Alb α_2	—0.176	—0.172	
Hb ESR SI α_2	—0.245*	0.018	
Hb ESR Alb SI α_2	—0.190	0.038	

Table VI (continued)

SI Alb	0 386***	0 569***	No significance
SI Alb Hb	0 318**	0 388*	
SI Alb ESR	0 366***	0 346*	
SI Alb α	0 322***	0 379*	
SI Alb Hb ESR	0 319**	0 209	
SI Alb Hb α	0 389***	0 236	
SI Alb ESR α	0 327***	0 286	
SI Alb Hb ESR α	0 277**	0 165	
SI α	—0 236*	—0 531***	No significance
SI α Alb	—0 076	—0 301	
SI α Hb	—0 201*	—0 410**	
SI α ESR	—0 196*	—0 2.7	
SI α Alb ESR	—0 094	—0 105	
SI α Hb ESR	—0 196*	—0 159	
SI α Alb Hb	—0 077	—0 276	
SI α Alb Hb ESR	—0 107	—0 091	
SI ESR	—0 137	—0 688***	Significant P < 0 001
SI ESR Alb	0 034	—0 561***	
SI ESR Hb	—0 058	—0 604***	
SI ESR α_2	—0 0 9	—0 551***	
SI ESR Alb Hb	0 066	—0 534***	
SI ESR Alb α	0 065	—0 504**	
SI ESR Hb α	—0 010	—0 506**	
SI ESR Alb Hb α	0 080	—0 483**	
ESR α	0 475***	0 576***	No significance
ESR α Alb	0 350***	0 398**	
ESR α SI	0 460***	0 343*	
ESR α Hb	0 451***	0 496***	
ESR α Alb SI	0 349***	0 293	
ESR α Alb Hb	0 354***	0 384*	
ESR α SI Hb	0 455***	0 341*	
ESR α Alb SI Hb	0 368***	0 292	
ESR Alb	—0 4 .***	—0 531 **	No significance
ESR Alb SI	—0 409***	—0 301	
ESR Alb Hb	—0 364 **	—0 410**	
ESR Alb α	—0 .**	—0 .27	
ESR Alb SI Hb	—0 365***	—0 103	
ESR Alb SI α	—0 .**	—0 159	
ESR Alb Hb α	—0 21 *	—0 276	
ESR Alb SI Hb α	—0 .76*	—0 091	
Alb α	—0 449***	—0 578***	No significance
Alb α SI	—0 399***	—0 396**	
Alb α Hb	—0 475***	—0 493**	
Alb α ESR	—0 13	—0 403 *	
Alb α SI Hb	—0 377 *	—0 384*	
Alb α SI ESR	—0 071	—0 354*	
Alb α Hb ESR	—0 313**	—0 363*	
Alb α SI Hb ESR	—0 68**	—0 361*	

Table VII

Correlations between *total hemoglobin versus total circulating amount* of albumin and total serum protein 50 women and 11 men with rheumatoid arthritis Absolute values and values after correction for weight and body surface area

Variable	n	Mean	S D	r
Total albumin	50	115 4	26 4	0 63***
Total hemoglobin		456 6	73 4	
Total protein	50	224 2	41 0	0 57***
Total hemoglobin		456 6	73 4	
Total albumin/kg	50	2 01	0 44	0 57***
Total hemoglobin/kg		7 81	1 20	
Total protein/kg	50	3 80	0 81	0 47***
Total hemoglobin/kg		7 81	1 20	
Total albumin/m²	50	71 2	14 7	0 56***
Total hemoglobin/m		279 5	38 8	
Total protein/m²	50	138 3	24 1	0 51***
Total hemoglobin/m		279 5	38 8	
Total albumin/m	50	70 8	15 6	0 61***
Total hemoglobin/m		279 4	43 9	
Total protein/m	50	137 3	24 9	0 56***
Total hemoglobin/m		279 4	43 9	

protein administration resulted in a slight decrease in hemoglobin concentration, but the total hemoglobin fall was marked The anemia of low protein states was slightly microcytic and normochromic or slightly hypochromic The plasma iron was low even when the iron stores were well filled When the iron supply was low enough to produce iron deficiency, the iron deficiency and low protein anemia were cumulative

In the Minnesota experiment in humans Keys & al (14) found that after 24 weeks of semistarvation the hemoglobin concentration had decreased by about 23 per cent and the total hemoglobin by 29 per cent of the original value This agreed well with the reduction of 27 per cent in active tissue They also found a decrease in the plasma albumin concentration by 10 per cent although the decrease in circulating albumin

was only 2 per cent as the plasma volume had increased 8 6 per cent

Although the patients with rheumatoid arthritis cannot be said to have the same high degree of protein deficiency as the animals and patients in the papers just cited many parallels can be drawn between protein deficiency anemia and that of rheumatoid arthritis

The total circulating amount of albumin in our 50 women with rheumatoid arthritis (material 3) was decreased by 18 2 per cent compared with the 14 normal women as shown in Fig 1 The controls were taken from another material in this series (Chapter II) their mean value for circulating albumin was 141 1 g SD 17 3 g 50 arthritic women mean 115 4 g S D 26 4 g The total circulating protein was not decreased in the arthritic group (mean 224 2 g S D 41 0 g compared with the mean of 220 2 g S D 21 5 g in the control group) The decrease in the total circulating albumin (—18 per cent) is of the same magnitude as the decrease in hemoglobin concentration (—17 per cent) and total hemoglobin amount (—15 per cent) when the women with rheumatoid arthritis are compared with the controls

In our patient material there is a correlation be ween the hemoglobin concentration and total hemoglobin amount versus circulating albumin and also (in the case of total hemoglobin) when related to the body parameters weight area and length (Table VII)

In our patients with active rheumatoid arthritis and various degrees of anemia there is thus a correlation between the concentration of hemoglobin and serum iron versus serum albumin concentration There is no correlation between the hemoglobin and total serum protein concentrations (Table V) A correlation between the total circulating amount of hemoglobin and total amount of albumin has also been shown for the patients in whom these determinations were made

The concentration and total amount of circulating albumin are lowered rather considerably in patients with active rheumatoid arthritis and this decrease and the anemia run parallel with the clinical activity see e g Swedin & Bengtsson (34) who found a significant correlation between serum albumin concentration and E S R $r =$ —0 46 very similar to our —0 43 in the 104 women and —0 53 in the 44 men (Table V bottom)

There are many protein disturbances in rheumatoid arthritis but the only abnormalities consistent with a protein deficiency are the low concentration of albumin and the decrease in total circulating albumin The anemia in rheumatoid arthritis is very similar to the type of anemia described in connection with protein deficiency The weight loss observed by others (8 12) and us (Chapter II) in cases with active rheumatoid arthritis is consistent with a negative protein balance There is about the same decrease in circulating hemoglobin and albumin These findings have led us to consider the possibility of a pathogenetical connection between the lowered albumin and the anemia in rheumatoid arthritis Investigations are being made with labelled proteins to study this question

Summary

Patients with rheumatoid arthritis have been studied with regard to a possible relationship between anemia and abnormalities in serum proteins

Clinical and laboratory abnormalities indicating a protein deficiency in the arthritic patients are discussed

The laboratory results have been correlated with the anemia and it was found that the decrease in albumin concentration is of the same magnitude as the decrease in hemoglobin concentration, while the decrease in total circulating albumin is of the same magnitude as the decrease in total hemoglobin amount

This may indicate a pathogenetical relation between protein deficiency and anemia in patients with active rheumatoid arthritis

In keeping with other authors, significant correlations were found between the clinical activity of the disease and the elevated serum protein alpha$_2$ globulin

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Clinical and laboratory abnormalities indicating a protein deficiency in the arthritic patients are discussed

The laboratory results have been correlated with the anemia and it was found that the decrease in albumin concentration is of the same magnitude as the decrease in hemoglobin concentration, while the decrease in total circulating albumin is of the same magnitude as the decrease in total hemoglobin amount

This may indicate a pathogenetical relation between protein deficiency and anemia in patients with active rheumatoid arthritis

In keeping with other authors, significant correlations were found between the clinical activity of the disease and the elevated serum protein alpha$_2$ globulin

This study was supported by *Konung Gustav V s 80 årsfond, Riksföreningen mot Reumatism* and *Karolinska Institutet*

CHAPTER VI

THE METABOLISM OF IODINF LABELLED TRANSFERRIN AND ALBUMIN

By *S Johansson L O Plantin O Strandberg*

Introduction

Evidence of a subnormal iron absorption in arthritic patients was presented in Chapter II The correlation between the absorption and erythrocyte utilization of radioiron versus the total iron binding capacity was significant for the female controls but not for the arthritic female patients (Chapter II Table V) Hallberg & Solvell (20) presented evidence suggesting that transferrin may play an important part in the control of absorption of iron from the gastro intestinal tract (cf Laurell 28) Their opinion was partly confirmed and extended by Charley et al (12) and also by Fisher & Price (16) Heilmeyer's (21) famous case with congenital atransferrinemia displayed absorption of iron from the gut and heavy deposition in the liver and other organs (though not so very much in the spleen) the patient had no iron in her bone marrow because iron could not be transported in the circulating blood owing to the absence of the specific iron binding protein

The total iron binding capacity (TIBC) which is an expression for the transferrin concentration is decreased compared with healthy subjects in the serum of patients with active rheumatoid arthritis This was first shown by Laurell (28) and confirmed by i a Brendstrup (9) and also by the results presented in Chapter II Ebaugh (15) reported normal or subnormal values in patients with rheumatoid arthritis and Jeffrey (24 25) found elevated TIBC values in his material of anemic arthritic patients Heilmeyer (21) noted that in all conditions associated with extensive inflammation there is always a decrease in total iron binding capacity and thus in the transferrin concentration

The albumin concentration in serum from patients with rheumatoid arthritis is also decreased as reported by many authors (for a review see Gutman 19) Decreased serum albumin conceontrations and decreased total circulating amounts of albumin have been demonstrated in Chapter V for arthritic patients together with a high correlation between the concentrations of albumin and hemoglobin as well as between total albumin and total hemoglobin

We decided to study the metabolism of transferrin and albumin labelled with I^{131} and I^{125} since the decreased concentration of these proteins may be related to the anemia in patients with rheumatoid arthritis The results suggested an increased degradation of the proteins

Material

Fifteen arthritic in patients [illegible] women and 6 men and 8 controls 4 women and 4 men were studied The transferrin metabolism was studied in 13 patients with rheumatoid arthritis and 6 controls and the albumin metabolism was studied in 9 patients with

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CHAPTER VI

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The albumin concentration in serum from patients with rheumatoid arthritis is also decreased as reported by many authors (for a review see Gutman 19) Decreased serum albumin concentrations and decreased total circulating amounts of albumin have been demonstrated in Chapter V for arthritic patients together with a high correlation between the concentrations of albumin and hemoglobin as well as between total albumin and total hemoglobin

We decided to study the metabolism of transferrin and albumin labelled with I^{131} and I^{125} since the decreased concentration of these proteins may be related to the anemia in patients with rheumatoid arthritis The results suggested an increased degradation of the proteins

Material

Fifteen arthritic in patients 9 women and 6 men, and 8 controls 4 women and 4 men, were studied The *transferrin metabolism* was studied in 13 patients with rheumatoid arthritis and 6 *controls* and the albumin metabolism was studied in 9 patients with

rheumatoid arthritis and 6 controls The patients had active (Shetlar & al 34), classical rheumatoid arthritis, according to the criteria of the American Rheumatism Association (1, 2)

None of the patients received treatment affecting the hematological system before or during the investigation e g blood transfusions, iron perorally or parenterally Only one patient had a very moderate long term systemic corticosteroid medication which was not changed before or during the study No subject had proteinuria The means of the data obtained for women and men are reported as a single group, owing to the relatively small number of subjects involved Some cases were excluded from this report because the curves for degradation rate (see below) showed a falling tendency, interpreted as a sign of denaturation of the labelled protein preparation injected

Methods

a Hematological methods

All the subjects were studied with routine hematological examinations, as described in the preceeding chapters During the study the total hemoglobin and blood volume were determined with the alveolar CO method (Chapter IV)

The plasma and blood volumes were also calculated by isotope dilution Labelled protein was injected into one arm and specimens of blood were taken from the other arm 6 and 9 minutes later The higher of these two values was used for calculating the plasma and blood volume according to Veall & Vetter (38), with their correction factor for extravascular distribution (6 minutes 1 010, 9 minutes 1 015)

The hemoglobin concentration, red cell count and hemotocrite in venous blood were determined twice a week during the test period as well as the serum total protein, paper electrophoresis serum iron concentration and total iron binding capacity, urine analysis was done weekly The TIBC was determined as follows serum was saturated with Fe SO_4 $(NH_4)_2$ SO_4 at pH 7 5 and surplus Fe SO $_4(NH_4)_2$ SO_4 was eliminated with an ion exchanger resin (Amberlite IRA 400) The iron content in the saturated serum was then determined with the same method as for serum iron The value for TIBC in serum in μg/100 ml multiplied by 0 0008 was used to obtain the transferrin concentration in g/100 ml (Koechlin 27, Jarnum & Lassen 23)

The sternal marrow was examined in most of the subjects with respect to morphology and storage iron content (see Chapter II) Paper electrophoretic analyses performed twice a week were used to determine the serum albumin concentration This was used for calculating the amount of intravascular albumin

b Protein preparations

The transferrin and albumin were obtained from AB Kabi Stockholm who stated that they were produced by Cohn fractionation of pooled human plasma

Transferrin In one part of the study the commercial transferrin preparation was further purified by Renee Norberg M D The commercial fraction was run in zone electrophoresis in polyvinyl chloride (Muller Eberhardt 31) see Fig 1 From this PVC block the beta fraction with the transferrin was isolated and labelled with iodine[125] The product was further purified by gel filtration in Sephadex G 200 according to Gelotte Flodin & Killander (17) The homogeneous

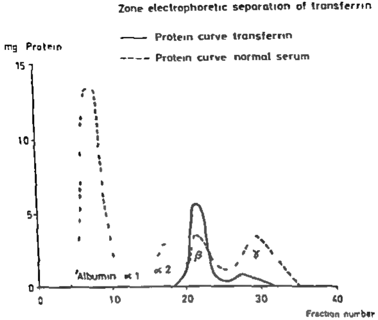

Fig 1
Preparative electrophoresis in polyvinyl chloride barbiturate buffer pH 8 6 from Cohn fraction IV (R Norberg)

fraction (from tubes 80—110 see Fig 2) was sterilised by filtration and tested for pyrogens and sterility

Labelling of the proteins was done according to Mc Farlane (30) The degree of iodination was about one atom I^{125} or I^{131} per molecule of protein

c Procedure for the metabolic studies

The preparations labelled with I^{131} were used within 3 weeks in order to minimize denaturation (polymerization) from the ionizing effect of self irradiation

Five controls and 7 patients with rheumatoid arthritis received albumin and transferrin in one and the same injection I^{131} labelled transferrin and I^{125} labelled albumin were used to start with but transferrin turned out be more liable to denaturation from self irradiation than albumin we changed to I^{125} transferrin and I^{131} albumin

The radioactive dose given was 25—35 μC for both I^{125} and I^{131} the amount of labelled protein did not exceed 10 mg

Thyroid blocking was done with about 0 3 g sodium iodide in solution daily one or two days before and during the whole study Blood samples were drawn daily the first week and every second day during the next two weeks The subjects were thus followed for three weeks The urine was collected quantitatively for every 24 hour period for 3 weeks 4 ml samples of plasma and urine were measured in a well crystal scintillation detector (Tracerlab P 20 BW) connected to

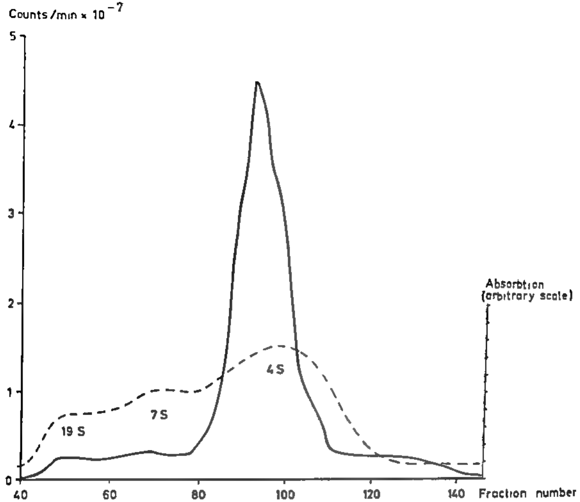

Fig 2

Gel filtration of I[1 5] transferrin in Sephadex G 200 column 0 05 M phosphate buffer pH 7 4 (R Norberg)

Unbroken line = radioactivity curve for transferrin fraction

Broken line = absorbancy at 254 mμ for normal serum

The sedimentation constants from analytical ultracentrifugation are indicated

a Versamatic II Scaler Spectrometer As two isotopes were used in most of the experiments the spectrometer was set for the respective gamma photopeak maxima (0 36 Mev for I^{131} and 0 035 Mev for I^{125}) Fecal specimens were measured directly in special (paper) containers in a liquid scintillation counter (Armac type) specially designed by Packard Inc for large specimens

A sufficient number of counts was registered to ensure an error not greater than ± 2 per cent Correction for radioactive decay was made by comparison with appropriate standards

Steady state was assumed in both groups of subjects studied Albumin and transferrin serum concentrations remained constant during the study

d Calculations

The following methods were used for analysis of the data

(1) The equilibrium time method (Campbell & al 11 Veall & Vetter 38)

(2) Compartment analysis (Matthews 29)

The calculations were programmed in ALGOL and run on a digital computer BESK or Facit EDB (Statskontoret) The computer turns out a table giving daily values for the percentage of the dose present in plasma and excreted in urine the cumulative total excretion the retained fraction the fractional catabolic rate the extravascular fraction and the results of the compartment analysis Closed three or four compartment systems were used as a mathematical model for the calculations of the transfer rates catabolism and distribution of the proteins Which system to use was decided from the computer s reliability tests of the data Further details of the computer program are to be published (Plantin 1966)

Intravascular (i v) pool was determined by multiplying the serum concentration of the protein and the plasma volume determined by the isotope dilution technique

Extravascular (e v) pool and total pool were calculated according to the equilibrium time or compartment method mentioned above

Retained dose for a given day was calculated from the cumulative activity excreted in the urine subtracted from the dose given

The degradation rates of the labelled proteins (in per cent of i v pool) for each 24 hour period were calculated by dividing 100 times the amount of the isotope excreted via the urine by the average amount remaining in the plasma during this period The i v amount of isotope was used and not the calculated total amount it was considered that a measured reference would be more reliable than a calculated one

Since the amount of radioactivity in the feces was always insignificant (< 0.5 % of the dose during the first week) only the urine excretion was taken into account The degradation rate for each subject was calculated from the 5th day to the end of the investigation

Results

a Hematological data

The anthropometric and hematological data for the controls and patients are listed in detail in Tables I and II Table III gives the differences between the means for patients and controls with women and men taken together The results are entirely in accordance with those demonstrated and discussed in the preceeding chapters From Table I it is clear that bone marrow iron in the controls could be demonstrated both histochemically and chemically Table II shows that 11 out of 15 patients with rheumatoid arthritis had histochemically demonstrable bone marrow iron and that 3 patients (Nos 4 10 12) had large amounts of storage iron in their bone marrow perhaps owing to previous blood transfusions (given $^1/_2$—1 year before the present study)

Four patients (Nos 2 6 11 13) had slight signs of iron deficiency with a low saturation percentage of the transferrin

b Plasma volumes

Table IV gives the means of the plasma volumes for patients and controls The means were close to those reported in Chapter IV (Table II 14) and displayed no significant difference between the arthritic patients and the controls (cf Chapter IV)

Table 1

Anthropometric and hematological data Healthy controls, 4 women and 4 men

Case	Age years	Height cm	Weight kg	Body area m²	ESR mm/hour	Hb g/100 ml	RBC ×10⁶	Corr PCV %	MCH μμg	MCV μ³	MCHC %	Total Hb g	Serum iron μg/100 ml	TIBC μg/100 ml	Saturation of TRF %	Transferrin conc g/100 ml	Albumin conc g/100 ml	Bone marrow iron: Histochemical	Bone marrow iron: mg/100 g marrow
										Females									
1	19	154	55 7	1 53	—	12 2	3 83	37 7	31 9	93 7	34 0	425	130	377	34 5	0 302	5 16	0	15 4
2	24	164	66 0	1 72	—	12 8	4 11	38 6	31 2	93 9	32 6	470	104	380	27 4	0 301	4 81	(+)	16 0
3	46	168	64 9	1 74	10	11 7	4 09	35 2	29 3	86 8	33 4	481	55	435	12 6	0 318	5 06	0	25 5
4	58	153	71 0	1 69	9	12 5	4 15	38 0	30 5	88 4	34 3	520	70	372	18 8	0 298	4 91	++	11 8
										Males									
5	22	176	61 0	1 78	6	14 3	4 86	42 9	29 4	89 3	33 3	610	97	355	27 3	0 291	5 09	0	9 5
6	22	182	69 4	1 89	1	16 6	5 44	51 3	30 1	94 3	32 3	—	156	417	37 4	0 331	5 06	+	5 0
7	22	173	—	—	—	15 7	5 25	45 0	31 3	86 0	33 8	—	—	—	—	—	5 14	+	1 9
8	63	170	71 0	1 82	9	13 9	4 42	42 6	31 5	96 5	32 8	695	125	325	38 4	0 260	5 16	—	—

Table II

Anthropometric and haematological data. Patients with rheumatoid arthritis: 9 women and 6 men

Case	Age years	Height cm	Weight kg	Body area m²	ESR mm/hour	Hb conc g/100 ml	RBC × 10⁶	Corr PCV	MCH µµg	MCV µ³	MCHC %	Total Hb g	Serum iron µg/100 ml	TIBC µg/100 ml	Satur transf %	Transferrin conc g/100 ml	Albumin conc g/100 ml	Clinical activity I—IV (Sl etlar & al 1956)	Bone marrow iron: Histochemical	Bone marrow iron: mg/100 g marrow
Females																				
1	57	155	40.6	1.44	38	10.7	3.87	35.0	27.6	90.8	30.4	335	27	35	11.5	0.188	3.89	III	+	17.8
2	61	159	19.0	1.47	53	10.1	3.39	32.8	9.5	96.8	30.8	336	17	289	5.9	0.231	3.80	IV	2+	13.0
3	55	154	32.1	1.21	18	10.9	3.90	38.3	6.7	—	29.2	—	—	—	—	—	[illegible]	III	—	—
4	60	157	62.1	1.62	17	11.2	3.60	37.4	30.6	106.5	30.2	—	89	—	—	0.185	4.02	III	1+	63.0
5	[illegible]	155	57.9	1.56	46	[illegible]	3.82	36.8	31.1	96.5	33.0	427	[illegible]	271	17.0	0.217	3.90	III	+	7.2
6	46	167	19.2	1.55	39	10.4	3.58	34.1	9.2	96.8	30.3	390	8	385	7.3	0.308	3.87	II	0	5.2
7	70	151	65.7	1.64	72	12.5	4.33	38.5	9.0	89.3	32.6	485	55	234	[illegible]	0.187	4.52	II	3+	15.0
8	52	165	74.2	1.81	96	12.7	4.35	38.9	9.6	91.0	[illegible]	[illegible]	47	265	17.8	0.212	4.61	II	0	—
9	55	165	15.0	1.46	22	11.8	4.06	38.3	29.2	90.3	30.9	130	[illegible]	282	24.6	0.226	4.53	III	+	—
Males																				
10	[illegible]	181	59.9	1.77	131	11.1	3.06	34.3	36.4	112.2	32.5	—	121	[illegible]	[illegible]	0.06	3.12	III	1+	[illegible]
11	51	187	86.5	[illegible]	90	[illegible]	4.49	39.8	27.9	88.7	31.5	710	28	93	9.6	0.234	3.47	III	+	—
12	63	168	65.0	1.77	59	12.2	4.00	38.1	30.5	95.6	31.9	545	67	329	[illegible]	[illegible]	3.88	IV	1+	69.8
13	43	160	48.0	1.47	[illegible]	10.4	3.84	33.6	27.1	88.3	31.0	410	20	232	8.7	0.182	3.86	III	[illegible]	8.7
14	50	175	65.7	1.90	64	[illegible]	4.04	39.8	31.9	98.6	32.5	735	47	[illegible]	18.0	[illegible]	[illegible]	II	0	—
15	54	187	99.0	[illegible]	53	13.4	4.26	41.9	31.5	99.2	32.1	800	0	[illegible]	[illegible]	0.213	3.96	III	[illegible]	14.3

Table III

Hematological data

Means for patients with rheumatoid arthritis (R A) and controls (C)

Differences between means

		n	Mean	Difference
Age years	C R A	8 15	34 5 56 2	21 7***
Length cm	C R A	8 15	167 5 165 9	1 6
Weight kg	C R.A	7 15	66 0 56 0	10 0
Body surface area	C R A	7 15	1 74 1 65	0 09
ESR mm/hour	C R A	5 15	7 0 62 4	55 4***
Hb g/100	C R A	8 15	13 7 11 7	2 0 *
$RBC \times 10^6$	C R A	8 15	4 52 3 90	0 62**
Corr PCV %	C R A	8 15	41 4 37 2	4 2*
MCH $\mu\mu g$	C R A	8 15	30 7 29 9	0 8
MCV μ^3	C R A	8 14	91 0 95 7	4 7
MCHC %	C R A	8 12	33 3 31 4	1 9**
Total hemoglobin g	C R A	6 12	534 521	13
Serum iron μg/100 ml	C R A	7 14	105 3 52 4	52 9*
TIBC μg/100 ml	C R A	7 13	380 279	101***
Saturation percentage of transferrin	C R A	7 13	28 1 18 3	9 7
Transferrin concentration g/100 ml	C R A	7 14	0 304 0 220	0 084***
Albumin concentration g/100 ml	C R A	8 15	5 09 3 97	1 12***

Table IV

Means for the plasma volumes determined with the alveolar carbon monoxide method (COHb) and isotope dilution methods Transferrin (TRF) and albumin (ALB) Controls and patients with reumatoid arthritis The means for ten subjects in whom the plasma volume was determined with all three methods are given in the lower part of the table

Method and subjects	Sex	n	Mean litres	S D
COHb Controls	F+M	6	3.09	0.35
COHb R A	F+M	12	3.14	0.58
TRF Controls	F+M	7	3.09	0.41
TRF R.A	F+M	13	3.45	0.76
ALB Controls	F+M	6	2.94	0.37
ALB R A	F+M	8	2.96	0.76
COHb Controls+R.A	F+M	10	3.15	0.52
TRF Controls+R.A	F+M	10	3.37	0.79
ALB Controls+R.A	F+M	10	3.16	0.87

Table V

Mean intravascular transferrin and albumin in patients with rheumatoid arthritis and controls with the statistical significances of the differences between the means for the two groups

		n	g	g/kg	g/m	g/m
I v transferrin	Controls	7	9.37	0.142	5.38	5.61
	Rheum arthr	13	7.74	0.128	4.56	4.58
	Difference		1.63	0.014	0.82	1.03
I v albumin	Controls	6	157.3	2.29	86.5	92.5
	Rheum arthr	9	113.5	1.90	67.1	67.5
	Difference		43.8**	0.39	19.4**	25.0**

Three methods for estimating the plasma volume (alveolar carbon monoxide isotope dilution with iodine labelled transferrin and with albumin) were compared in 10 subjects in whom all three methods were used (Table IV lower part) There was no significant difference between the means for the three methods This comparison has been briefly discussed in Chapter IV

c Intravascular transferrin and albumin

Table V shows the means for intravascular transferrin and albumin in the patients and controls The mean intravascular trans

Table VI

Means for extravascular and total pools of transferrin and albumin calculated from (1) equilibrium time (2) compartment analysis methods and e v /i v ratio for each method Patients with rheumatoid arthritis and controls

	n	Equilibrium time			Compartment analysis		
		e v	Total	e v /i v	e v	Total	e v /i v
Transferrin							
Controls	7	18 8	28 2	1 94	10 9	20 3	1 17
Rheum arthr	13	10 6	18 4	1 41	7 7	16 2	1 02
Albumin							
Controls	6	220	374	1 39	183	340	1 19
Rheum arthr	9	172	286	1 54	147	261	1 33

Table VII

Mean degradation of transferrin and albumin in patients with rheumatoid arthritis and controls with the statistical significances of the differences between the means for the two groups

		n	Per cent of i v pool	g/24 h	g/kg/24 h	g/m /24 h	g/m/24 h
Transferrin degradation	Controls	7	10 56	0 949	0 0144	0 547	0 570
	Rheum arthr	13	19 22	1 479	0 0243	0 868	0 875
	Difference		8 66***	0 530**	0 0099**	0 321**	0 305**
Albumin degradation	Controls	6	5 97	9 21[1]	0 126[1]	4 28	5 44
	Rheum arthr	9	11 02	11 90	0 213	7 26	7 12
	Difference		*5 05**	*2 69*	*0 087*	*2 98**	*1 68*

[1] 5 subjects

ferrin was non significantly lower for the arthritic subjects (mean 7 74 g S D 2 1) than for the controls (mean 9 37 S D 1 9)

The means for intravascular albumin were significantly (***) lower for the arthritic subects than for the controls As the arthritic subjects had a subnormal mean weight (cf Table III) the difference between the groups was smaller when the absolute mean i v albumin was related to weight and body surface area

d Extravascular and total transferrin and albumin

These values as well as the mean ratios for e v /i v pools for each method are shown

Table VIII

Means of degradation rates for transferrin and albumin grouped according to clinical activity of the rheumatoid disease (Clinical activity grouped according to Sharp & al 34)

Clinical activity group	n	Degradation rate expressed as % of iv pool	g/24 h	g/kg/24 h	g/m 4 h	g/m h
			Transferrin			
II	4	18 5	1 53	0 0 5	0 91	0 9
III	7	18 7	1 37	0 0	0 9	0 79
IV		2 6	1 75	0 031	1 07	1 0
			Albumin			
III	7	11 0	11 7	0 1	7 15	6 97
IV	2	11 0	12 5	[illegible]	7 65	7 63

in Table VI The figures in Tables VI and VII clearly illustrate the reduced pools in the arthritic subjects compared with the controls for both transferrin and albumin

e Degradation rate for the labelled proteins

Figures 3—5 show the plasma activity curves the curves for the fraction retained (total dose minus the activity excreted) and daily degradation rate for transferrin and albumin in controls and patients with rheumatoid arthritis

Table VII indicates that the transferrin degradation rate of the arthritic patients was significantly (***) higher than that of the controls expressed in per cent of the iv pool 24 h and g 24 h and also related to weight body surface area and height The mean albumin degradation rate expressed in per cent of the iv pool 24 h was higher ( ) for the arthritic subjects but only slightly higher when expressed in g/24 h

The clinical activity of the rheumatoid disease (classed according to Sharp & coworkers 34) showed no correlation with the degradation rate of transferrin and albumin (Table VIII)

A positive intercorrelation (r = 0 92 ** Fig 6) was found between the degradation rates of transferrin and albumin in patients and controls expressed in per cent of the iv pool /24 h The relative degradation rate of transferrin was about 1 7 times higher than that of albumin In absolute terms the albumin degradation rate was 8—10 times higher than that for transferrin the mean intravascular pool of albumin was about 15 times larger than the transferrin iv pool in the subjects studied

There was no *correlation between the degradation rate* in g/24 h and serum *concentrations of either transferrin or albumin* There was a positive correlation between ESR and the *relative degradation rates of* transferrin and albumin and a negative *correlation (r — 0 47*)* between the serum *iron concentration* and the degradation rate of transferrin in per cent of the iv pool but *not in* g 24 h

Table VI

Means for extravascular and total pools of transferrin and albumin calculated from (1) equilibrium time, (2) compartment analysis methods and e.v./i.v. ratio for each method Patients with rheumatoid arthritis and controls

	n	Equilibrium time			Compartment analysis		
		e.v.	Total	e.v./i.v.	e.v.	Total	e.v./i.v.
Transferrin							
Controls	7	18.8	28.2	1.94	10.9	20.3	1.17
Rheum arthr	13	10.6	18.4	1.41	7.7	16.2	1.02
Albumin							
Controls	6	220	374	1.39	183	340	1.19
Rheum arthr	9	172	286	1.54	147	261	1.33

Table VII

Mean degradation of transferrin and albumin in patients with rheumatoid arthritis and controls with the statistical significances of the differences between the means for the two groups

		n	Per cent of i.v. pool	g/24 h	g/kg/24 h	g/m²/24 h	g/m/24 h
Transferrin degradation	Controls	7	10.56	0.949	0.0144	0.547	0.570
	Rheum arthr	*13*	*19.22*	*1.479*	*0.0243*	*0.968*	*0.875*
	Difference		*8.66****	*0.530***	*0.0099***	*0.321***	*0.305***
Albumin degradation	Controls	6	5.97	9.21[1]	0.126[1]	4.28	5.44
	Rheum arthr	9	11.02	11.90	0.213	7.26	7.12
	Difference		5.05*	2.69	0.087	2.98*	1.68

1 5 subjects

ferrin was non significantly lower for the arthritic subjects (mean 7.74 g, S.D. 2.1) than for the controls (mean 9.37 S.D. 1.9)

The means for intravascular albumin were significantly (***) lower for the arthritic subects than for the controls As the arthritic subjects had a subnormal mean weight (cf Table III) the difference between the groups was smaller when the absolute mean i.v. albumin was related to weight and body surface area

d Extravascular and total transferrin and albumin

These values as well as the mean ratios for e.v./i.v. pools for each method are shown

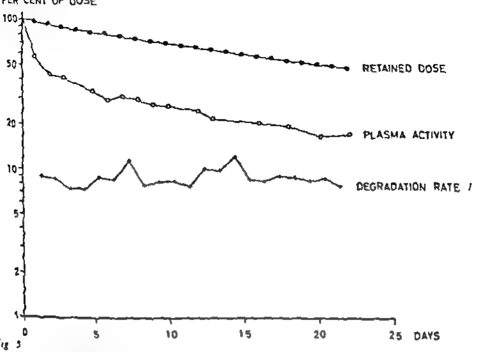

Fig 5
Female patient with rheumatoid arthritis (No 2) Plasma activity curve and the calculated curves for retained dose and degradation rate of I^{125} labelled albumin

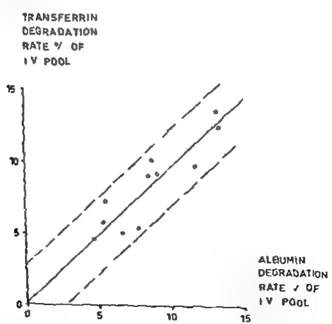

Fig 6
Seven patients with rheumatoid arthritis and five controls Correlation between the degradation rate, in per cent of intravascular pool for albumin (x) and transferrin (y)
The regression line ± 2 S D is indicated
r = 0 9 **
Equation for the regression line
y = 1 9 5 x + 0 03

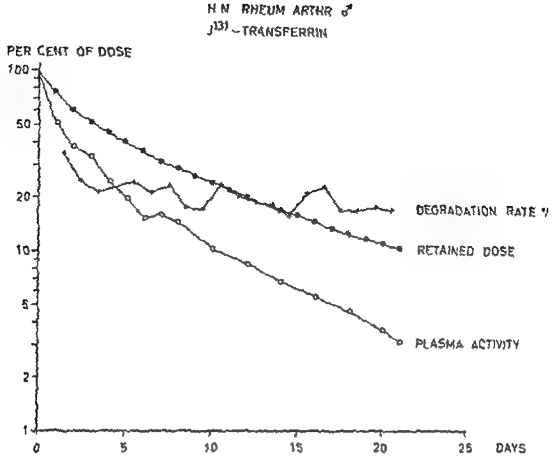

Fig 3
Male patient (No 11) with rheumatoid arthritis. *Plasma activity curve and the calculated curves fo* retained dose and *degradation rate* of I^{131} labelled transferrin

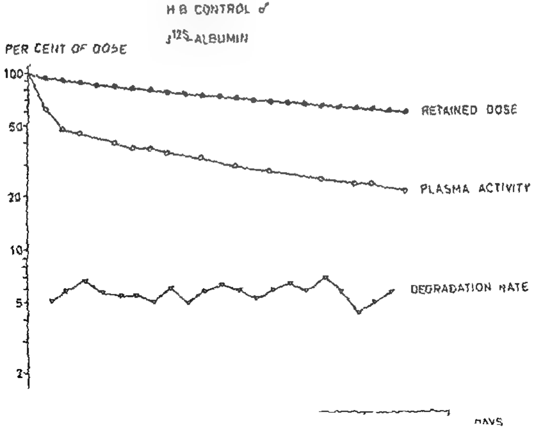

Table IX

Metabolism of transferrin

Comparison between figures from earlier studies and the present one

Authors	Subjects	n	Intravascular pool g	Intravascular pool g/kg	Intravascular pool g/m	T½ days from plasma elimination curve	Degradation rate %/24 h	Degradation rate g/24 h	Degradation rate g/kg/24 h	Degradation rate g/m²/24 h
Awai & Brown (3)	Controls M	9	5.9			8.9	7.9	0.85	0.0118	
Awai & Brown (3)	Rheum arthr	1	1.54—1.7			7.5	9.?	0.??	0.0175	
Katz (6)	Controls M	8		0.181		7.6			0.??1	
Jarnum & Lassen (3)	Controls M	11	1	0.193	7.0	8.7	18.?[1]	2[3]	0.035[3]	1.76
Jarnum & Lassen (3)	Rheum arthr	3	12.0[2]	0.231	6.9		21.?[1]	2.5[3]	0.048[3]	1.1
Present authors	Controls F+M	7	9.1	0.112	5.38	7.1	10.6[1]	0.95	0.0114	0.55
Present authors	Rheum arthr F+M	13	7.7	0.1?9	4.56	3.7	19.2[1]	1.18	0.0213	0.87

[1] Degradation rates calculated from intravascular pool

[2] Calculated from total transferrin pool

[3] Calculated from figures given by the authors cited

Discussion

a Protein preparations

The labelled transferrin preparation, after purification, showed a single homogeneous gradient in electrophoresis and gel filtration, it was immunologically pure as demonstrated in an Ouchterlony gel diffusion test and immune electrophoresis against rabbit anti human serum, and seemingly undenaturated The ultimate proof of metabolic homogeneity was the constant catabolic rate throughout the investigation

The albumin preparation used has been reported on in detail by Wetterfors (39) It was found that one of the albumin preparations contained aggregates heavier than 7 S when subjected to gelfiltration This preparation displayed a decreasing degradation rate during the first week when injected in patients and controls, making it impossible to apply Matthew s analysis After the first week when the metabolic rate was constant it would have been possible to calculate the degradation rate However, such cases with a decreasing degradation rate were not included in the present material

b Subjects investigated

Only one patient (Table II, No 6) was treated with a low dose of systemic corticosteroids (2 5 mg prednisolone/day) during the test period This patient s transferrin metabolism did not deviate from those of the other patients Berson & al (6) reported that the albumin metabolism was possibly increased in patients with rheumatoid arthritis treated with systemic corticosteroids The same was stated in a recent report by Wilkinson & al (40) Glass & al (18) reported that the albumin metabolism was influenced by systemic corticosteroid therapy through increased leakage from the stomach. This was assumed from the results of two patients with rheumatoid arthritis examined before and during steroid treatment

The patients in the present study were considered to be in a steady state, as there were no changes at all in the serum concentrations of total protein albumin or transferrin, nor in the hemoglobin concentration red cell count and hematocrit, which were all controlled twice a week throughout the test The ESR in the patient group was controlled every week and showed no essential changes, this was taken to indicate a constant clinical activity during the test period (see e g Shetlar & al 34, Bottiger & al 10) Nor did repeated controls reveal any changes in the patients clinical activity during the test

c Transferrin metabolism

This technique seems not to have been used previously to study a substantial number patients with rheumatoid arthritis Some data from the literature are summarized in Table IX concerning metabolic studies on iodine labelled transferrin Our own figures for the intravascular amounts of transferrin agree with the results published earlier

The transferrin degradation expressed in g/kg/24 h seems rather low more in agreement with the figures of Awai & Brown than with those of Katz and Jarnum & Lassen

d Albumin metabolism

Table X (partly from Wetterfors 39) summarizes intravascular albumin pools (related to body weight) and degradation of albumin in a large number of papers together with a few studies from patients with rheumatoid arthritis The figures for mean iv albumin per kg body weight in the pre

diminished intravascular extravascular and total amounts of the proteins found in the patients with rheumatoid arthritis suggest that the catabolism had been higher than the synthesis in an earlier phase of the disease The imbalance between catabolism and synthesis may then have become equalized in a later stage of the disease by an increase in the synthesis In the case of transferrin there was an increase both in the absolute and in the relative degradation rate during the period of the study In the case of albumin there was an increase in the relative degradation rate but the low intravascular pool resulted in an absolute degradation rate within normal limits

The present series showed a significant correlation between the relative degradation rates of transferrin and albumin (*Fig 6*) In this connection it is of interest to note that Olhagen & al (32 and Birke & al (7) have demonstrated hypercatabolism of gamma globulin in patients with rheumatoid arthritis systemic lupus erythematosus and Sjogren s syndrome The present findings agree with those of Jarnum & Lassen (23) who found the same correlation between the relative degradation rate of transferrin and albumin in patients with infectious toxic states their controls did not deviate from the regression In the present series the degradation of transferrin and albumin has been correlated ■ the hemoglobin and serum iron concetrations ESR and (for transferrin) the percentage saturation of transferrin The positive correlations between ESR and the fractional degradation rates of transferrin and albumin may reflect the activity of the disease although there was no correlation between the activity ■ judged by clinical criteria and the catabolism of the two proteins (Table VIII)

Awai & Brown (3) found a high correlation ($r = +0.83$) between total transferrin concentration (mg/kg) and transferrin degradation (mg/kg/day) in 33 subjects representing 9 controls 7 patients with iron deficiency and a group comprising various disorders On the other hand infusion of relatively large amounts of transferrin which raised the plasma and total body transferrin levels to more than twice the normal values did not change the distribution within the body nor did it appreciably affect the absolute amounts of transferrin degraded each day We did not find any significant correlation between the degradation of transferrin or albumin and the serum concentrations of the two proteins This ■ understandable since these serum concentrations are low in actively diseased patients (see e g Chapter V) whereas the degradation of the protein is higher in arthritic than in healthy subjects

The pathological metabolism of albumin resulting in a decreased i v amount was shown to be correlated to the hemoglobin concentration and total hemoglobin (Chapter V) The patients with *rheumatoid arthritis* have a low serum iron concentration and a decreased uptake of iron from the gastrointestinal tract but they have at least a normal unbound iron binding capacity in the serum (Chapter II) Further they have a normal quantitative plasma transport of transferrin bound iron (Ebaugh 15) mostly storage iron in the sternal marrow (Chapters II III Table II) they utilize the absorbed iron normally (Chapter II) Whatever the *relation* between a pathological protein metabolism and the anemia, it does not seem to be mediated by a defective iron absorption due to low transferrin values

Table X

Metabolism of albumin
Comparison between figures from different authors

Authors	Subjects	n	Intra vascular pool g/kg	Degradation	
				% of i v pool	g/kg/24 h
Sterling (36)	Controls	21	—	6 6[2]	0 233
Berson & al (6)	Controls	3	1 97	10 3[2]	0 200—0 215
Cohen & Schamroth (13)	Controls	5	1 36	8 8—10 2[1]	0 125
Steinfeld (35)	Controls	12	1 40	4 6[2]=12 6[1]	0 180[2]
Steinfeld (35)	Controls	8	1 70	5 22=13 8[1]	0 236[2]
Jarnum & Schwartz (22)	Controls	20	2 12	10 0[1]=3 9[2]	0 206
Cohen & al (14)	Controls	6	1 78	8 8—10 3[1]	0 185[1]
Beeken & al (5)	Controls	13	1 68	4 68[2]=10[1]	0 225[2]= =0 196[1]
Takeda & Reeve (37)	Controls	13	1 60	8 9[1]	0 142
Wetterfors (39)	Controls	15	2 00	8 9—9 8	0 175—0 186
Berson & al (6)	Rheum arthr	9	1 96	5 8[2]	0 279[2]
Jarnum & Lassen (23)	Controls	12	3 14[3]	9 3[1]	0 284[3]
Jarnum & Lassen (23)	Rheum arthr	3	3 32[3]	6 2—10 4	0 291[3]
Wilkinson & al (40)	Rheum arthr normal range	8	1 50	16 3[1] 10 1—15 4	0 244[3]
Present authors	Controls	6	2 30	6 0[1]	0 126
	Rheum arthr	9	1 90	11 9[1]	0 213

[1] Degradation rates calculated from intravascular pool
[2] Calculated from total albumin pool
[3] Calculated from figures given by the author cited

sent control series seem rather high, being exceeded only by those of Jarnum & Lassen This may conceivably be due to our use of paper electrophoresis for determining the serum albumin concentration, this method gives high values

The means for the relative and absolute degradation of albumin in the present series of patients and controls do not deviate significantly from those of series published earlier Wilkinson & al (40) have reported the lowest mean for intravascular pool and rather high metabolic rates Berson & al (6) found the highest degradation of albumin in arthritic patients 0 279 g/kg/24 h but their series includes four patients on systemic corticosteroid therapy

During this study the synthesis and catabolism were probably equal in the patients with rheumatoid arthritis since they were presumably in a steady state Since a hypercatabolism of albumin and especially of transferrin was demonstrated there must have been an increase in the synthesis The

diminished intravascular extravascular and total amounts of the proteins found in the patients with rheumatoid arthritis suggest that the catabolism had been higher than the synthesis in an earlier phase of the disease The imbalance between catabolism and synthesis may then have become equalized in a later stage of the disease by an increase in the synthesis In the case of transferrin there was an increase both in the absolute and in the relative degradation rate during the period of the study In the case of albumin there was an increase in the relative degradation rate but the low intravascular pool resulted in an absolute degradation rate within normal limits

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Summary

The metabolism of iodine labelled transferrin and albumin has been studied in a group of patients with rheumatoid arthritis and in a control group

The intravascular, extravascular and total amounts of both proteins were subnormal in the patient group, especially for albumin

The patient group showed an increased degradation rate of transferrin compared with the controls

In the patients with rheumatoid arthritis the relative degradation rate of albumin was increased whereas the absolute amount degraded per day was only slightly increased

The decrease in circulating and total amounts of transferrin and albumin can probably be ascribed to an increased catabolism which in an early phase of the disease is higher than the synthesis

Acknowledgements

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CHAPTER VII

THE INFLUENCE OF CORTICOSTEROID THERAPY ON HEMATOLOGICAL VALUES BONE MARROW IRON AND IRON ABSORPTION IN PATIENTS WITH RHEUMATOID ARTHRITIS

by O *Strandberg*

Introduction

The positive influence of corticosteroid therapy on the hemoglobin concentration in patients with rheumatoid arthritis was pointed out already by Hench & al (20) The initial elevation of the hemoglobin concentration during such therapy has subsequently been confirmed with larger groups of patients by Layani & al (25) Empire Rheumatism Council (10) West (38) Fladee & al (12) Nuffield Foundation (24)

These papers report a moderate elevation in the hemoglobin concentration (and in some reports an increased number of red cells as well) when patients with rheumatoid arthritis received dosages of corticosteroids that gave clinical improvement and depression of ESR However in the reports from the Empire Rheumatism Council and the Nuffield Foundation the mean hemoglobin concentrations of the corticosteroid group and the controls did not differ when the therapy was given for more than 2 years This may be relevant to the discussion of changes in bone marrow storage iron (see below)

In hematologically normal children long term steroid treatment of bronchial asthma produces significantly higher values for hemoglobin concentration red blood cell and packed cell volume but not a significant change in the mean corpuscular hemoglobin mean corpuscular volume and mean corpuscular hemoglobin concentration in comparison with asthmatic children not receiving steroids (Agarwal 1 3) An increase in the total hemoglobin mass was also reported in the steroid group (Agarwal 2) The reported increases in the hematological values were moderate with no tendency to polycythemia There are several reports of changes in the bone marrow cytology due to corticosteroid treatment of patients with rheumatoid arthritis e g Havermark & Nordensson (21) Jasinski & Staechlin (22) Layani & co-workers (25) and Gross & Seiche (18) Berglund Nordensson & Olhagen (6) reviewed the literature with respect to hyperfunction of the reticuloendothelial system in patients with rheumatoid arthritis and made careful morphologic (bone marrow) biochemical and serologic studies before and during corticosteroid therapy in two cases with very active rheumatoid disease They found that corticosteroid therapy led to a normalisation of the initial hyperplasia of R E elements especially plasma cells in the bone marrow that high gamma globulin approached normal levels and that raised serological titres decreased

As stated above there are many publications concerning the influence of corticoste

Table I

Anthropological and clinical data

No	Sex	Age (years)	ESR at the beginning of the trial	ESR after six weeks corticosteroid treatment	Duration of disease (years)	Titer of rheum factor	Clinical activity[3]	Previous therapy[1] Bt	Au	Fe parenteral	Fe oral	St	Pb	Cq	Steroid preparation during 2nd part of trial
1	F	30	45	20	20	1 512	II	+	(+)		+			+	Dexamethazone 0 5 mg x 3
2	F	31	43	28	23	1 32768	IV	+	+		+		+		Dexamethazone 0 5 mg x 3
3	F	37	125	80	6	1 1024	III		+	+	+				Dexamethazone 0 5 mg x 3
4	F	31	42	26	3	1 2048	II	+		+	+			+	Paramethazone 1 mg x 3—2
5	F	15	117	111	1	1 128	IV								ACTH prolonged effect 30 IU/d
6	M	32	60	24	2	1 2048	II								Dexamethazone 0 5 mg x 3
7	M	18	105	46	4	1 4096	III			+	+	(+)[2]	+	+	Betamethazone 0 25 mg x 1 +30 IU ACTH prol /week
8	M	60	83	38	5	1 8192	III			+			+	+	Methylprednisolone 4 mg x 3
9	M	47	100	75	½	1 2048	IV								Prednisolone 5 mg x 3
10	M	66	68	47	6	1 1024	III				+			+	ACTH prolongat 45 IU/d

[1] Treatment with Bt — blood transfusions
Au — gold
Fe — iron
St — steroids
Pb — phenyl butazone
Cq — chloroquine

[2] The patient had received some injections of ACTH a year before the trial

[3] According to Shetlar et al (32)

roid treatment on hematological values and bone marrow cytology, reports dealing with iron absorption in connection with the administration of corticosteroids (Swanson & Bauer 35) do not seem to be so frequent This paper reports changes in hematological values bone marrow iron amount and iron absorption and utilization in a group of patients with active rheumatoid arthritis before and during six weeks systemic treatment with corticosteroids As an effect of the steroid treatment the hematological values improved the iron absorption from the gastrointestinal tract increased and the storage iron in the bone marrow was mobilized

Material

Ten in patients were studied 5 women and 5 men with definite and classical active rheumatoid arthritis according to the American Rheumatism Association criteria (4 5) Their clinical activity was classified according to Shetlar & al (32) All had positive rheumatoid factor test No systemic corticosteroid therapy had been given prior to the study Most patients had received local injections of corticosteroids now and then but not during the actual period of investigation Some data on the patients are given in Table I

Four of the patients received dexamethazone (1 5 mg daily) two ACTH gel (30 and 45 IU/day respectively) one paramethazone (3 mg/day) and one prednisolone (15 mg/day one patient (No 8) had a rather large dose of methylprednisolone (20 mg/day) and one (No 7) had betamethazone (1 mg daily) Five of the patients are described in Chapter II

Methods

Conventional hematological methods were used (Chapter II) Blood volume and total hemoglobin determinations were done with the alveolar carbon monoxide method (Sjöstrand 33) Sternal marrow iron was estimated in micro sections according to Rath & Finch (29) and chemically according to Stenninger & Brante (34)

The iron absorption was estimated with oral iron tolerance test and with Fe^{59} absorption measured by the fecal recovery method The erythrocyte utilization of the absorbed Fe^{59} was determined 2—3 weeks after the administration of the radioiron For details see Chapter II

Statistical method For every subject the difference was calculated between the values for each variable before and during steroid therapy The mean changes are given in the tables These changes were checked for the significance of their difference from zero by the t test

Plan of the investigation During a 3 week control period without corticosteroid treatment the patients were studied with respect to hematological values total hemoglobin volumes of blood plasma and red cells and iron absorption

The same variables were studied again after six weeks treatment with corticosteroids

Routine physiotherapy and salicylates were given to the patients throughout the investigation (cf Scott & al 31)

Results

a ESR

Tables I and II show that the mean ESR decreased significantly (xxx) during the 6 weeks steroid treatment Only one patient

Table II

Hematological values. Means for ten patients with rheumatoid arthritis untreated (U) and treated (T) with corticosteroids with the statistical significance of the difference between the means

		Mean	SD	Difference	SD (diff)
ESR mm/h	U	78 6	10 1	[illegible]8 9***	17 1
	T	49 8	9 7		
Hemoglobin conc g/100 ml	U	10 6	1 0	0 7**	0 64
	T	11 3	1 4		
Number of red cells 10^6	U	3 7[illegible]	0 23	0 [illegible] *	0 33
	T	4 03	0 38		
Hematocrit %	U	34 9	3 0	3 1***	1 4
	T	38 0	3 [illegible]		
MCH $\mu\mu g$	U	[illegible]7 [illegible]	1 6	0 4	1 7
	T	28 0	2 1		
MCV μ^3	U	94 3	[illegible] 5	1 6	6 5
	T	95 9	8 0		
MCHC, %	U	30 4	0 9	0 5	1 [illegible]
	T	[illegible]9 9	1 9		
Reticulocytes %	U	[illegible]1 6	9 3	2 [illegible]	11 9
	T	3 8	12 3		

Table III

Serum iron total (TIBC) and unbound iron binding capacity (UIBC) and saturation per cent of TIBC. Means for ten patients with rheumatoid arthritis untreated (U) and treated (T) with corticosteroids with the statistical significance of the difference between the means

		N	Mean	SD	Difference	SD (diff)
Serum iron µg/100 ml	U	10	3[illegible] 6	[illegible]8 6	[illegible]3 4	39 4
	T	10	60 0	40 8		
TIBC, µg/100 ml	U	9	[illegible]61 6	41	46**	54
	T	9	336 [illegible]	64		
UIBC µg/100 ml	U	9	[illegible]1 4	39	50 0	5 8
	T	9	[illegible]1 9	84		
Saturation of TIBC per cent	U	9	14 7	10 6	5 5	16 5
	T	9	[illegible]	14 8		

Table IV

Total hemoglobin Means for ten patients with rheumatoid arthritis untreated (U) and treated (T) with corticosteroids

		Mean	SD	*Difference*	SD *(diff)*
Total hemoglobin g	U T	486 530	117 133	44	67 3
Total hemoglobin/kg g	U T	9 0 9 7	1 4 1 9	0 7	1 5
Total hemoglobin/m [illegible]	U T	304 330	58 72	26	46 0

had unaltered ESR after 6 weeks treatment with ACTH

b Hematological values (Table II)

The mean hemoglobin concentration increased from 10 6 to 11 3 g/100 ml which is *significant at the 1 per cent level Only* one patient displayed a lower hemoglobin concentration after the steroid course

The mean red cell count increased from 3 76 to 4 03 × 10⁶ Four patients showed unchanged values after the therapy

The packed cell volume increased more decidedly by 3 1 per cent from 34 9 to 38 0 per cent which is highly significant All patients showed *an increase in hematocrit* during the investigation The erythrocyte indices MCH MCV and MCHC did not change nor did the reticulocyte count

The total hemoglobin (Table III) increased only slightly during the period of observation

c Serum iron concentration and TIBC (Table IV)

An increasing tendency was obtained for serum iron and TIBC the latter rising significantly (xx) Both showed much the same percentage rise with the result that the percentage saturation of the to al iron binding *capacity only changed from 15 to 20 per cent*

d Blood plasma and red cell volumes (Table V)

No change was detected during the period *of therapy*

e Iron absorption tests (Table VI Fig 3)

The mean rise in serum iron concentration 2 hours after administration of 0 5 g ferrosi lactas changed from 9 to 67 μg/100 ml which was not statistically significant Two patients had unaltered *flat iron tolerance* curves

The Fe^{59} absorption from the gastrointestinal tract was studied in six patients before and during the administration of corticosteroids the mean absorption of the radioiron dose increased from 6 9 to 18 1 per cent

The mean erythrocyte utilization in per cent of the peroral dose of Fe^{59} *increased* significantly at the 5 per cent level from 5 8 to 14 5 per cent two patients had unchanged utilization figures No change was found in the erythrocyte utilization calculated as a percentage of the absorbed dose (cf Chapter II)

Table II

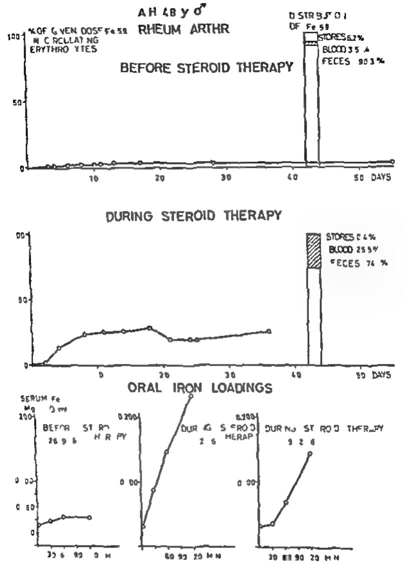
Hematological values. Means for ten patients with rheumatoid arthritis untreated (U) and treated (T) with corticosteroids with the statistical significance of the difference between the means

		Mean	SD	Difference	SD (diff)
ESR mm/h	U	78.6	10.1	28.8***	17.1
	T	49.8	9.7		
Hemoglobin conc g/100 ml	U	10.6	1.0	0.7**	0.64
	T	11.3	1.4		
Number of red cells 10^6	U	3.76	0.23	0.27*	0.33
	T	4.03	0.38		
Hematocrit %	U	34.9	3.0	3.1***	1.4
	T	38.0	3.2		
MCH $\mu\mu$g	U	27.6	1.6	0.4	1.7
	T	28.0	2.1		
MCV μ^3	U	94.3	6.5	1.6	6.5
	T	95.9	8.0		
MCHC %	U	30.4	0.9	0.5	1.6
	T	29.9	1.9		
Reticulocytes ‰	U	21.6	9.3	2.2	11.9
	T	23.8	12.3		

Table III

Serum iron, total (TIBC) and unbound iron binding capacity (UIBC) and saturation per cent of TIBC. Means for ten patients with rheumatoid arthritis untreated (U) and treated (T) with corticosteroids with the statistical significance of the difference between the means

		N	Mean	SD	Difference	SD (diff)
Serum iron μg/100 ml	U	10	36.6	28.8	23.4	39.4
	T	10	60.0	40.8		
TIBC, μg/100 ml	U	9	261.6	41	74.6**	54.2
	T	9	336.2	64		
UIBC μg/100 ml	U	9	221.4	39	50.0	75.8
	T	9	271.9	84		
Saturation of TIBC, per cent	U	9	14.7	10.6	5.5	16.5
	T	9	20.2	14.8		



F g

Pa ent No 7 Fe⁵⁹ abso pt on erythrocyte ut l zat on and oral ron tolerance test (lowe of *f gu e*) before and dur ng therapy w h betamethazone Compare th s f gure w th the t n F g 1

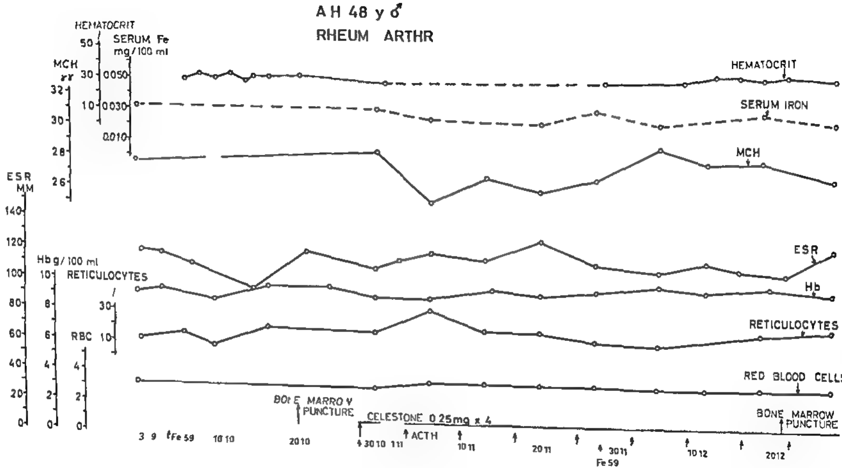


Fig 1

Patient No 7 ESR hemoglobin concentration red cell count hematocrit MCH reticulocyte count and serum iron concentration before and during therapy with betamethazone The patient received also 30 IU ACTH (prolonged action) once a week during the test period

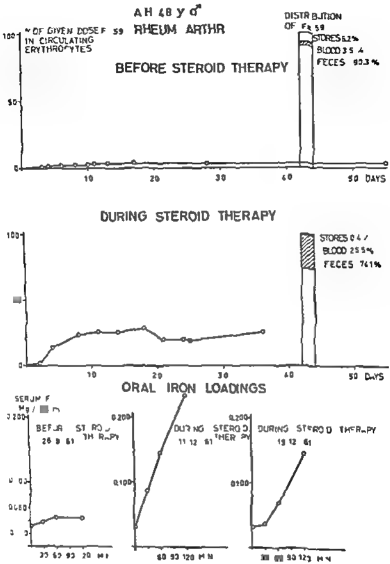


Fig 2

Patient No ~ Fe59 absorption erythrocyte utilization and oral iron tolerance test (lower part of figure) before and during therapy with betamethazone Compare this figure with the time axis in Fig 1

Table V

Blood plasma and red cell volumes Means for ten patients with rheumatoid arthritis untreated *(U) and treated (T) with corticosteroids*

		Mean	SD	*Difference*	*SD (diff)*
Blood volume l	U	4 9	1 0	*0*	*0*
	T	4 9	0 9		
Plasma volume l	U	3 3	0 6	0 11	0 36
	T	3 2	0 5		
Red cell volume l	U	1 6	0 4	0 14	0 22
	T	1 7	0 4		

Table VI

Iron absorption tests Means for patients with rheumatoid arthritis untreated (U) and treated (T) *with corticosteroids with the statistical significance of the difference between the means*

		n	Mean	SD	Difference	SD (diff)
Rise in serum iron oral tolerance test $\mu g/100$ ml after 2 hours	U	8	9 0	11 0	57 5	69 4
	T	8	66 5	77 3		
Absorption of Fe^{59} per cent of dose	*U*	*6*	*6 9*	4 8	11 2	12 4
	T	6	18 1	11 8		
Erythrocyte utilization of Fe^{59} per cent of dose	U	7	5 8	4 4	8 7*	7 5
	T	7	14 5	9 7		
Erythrocyte utilization of Fe^{59} per cent of absorbed dose	U	6	78 7	27 8	1 1	—
	T	6	77 6	22 7		

In one of the patients (No 5) the hematological data and ESR before and during steroid therapy (Fig 1) showed no essential changes However, the iron absorption measured with the tolerance test, increased and absorption of Fe^{59} increased from 10 to 26 per cent during the steroid therapy (Fig 2) The erythrocyte utilization of Fe^{59} also increased, from 3 5 to 25 5 per cent of the dose All the iron absorption tests are summarized in Fig 3

f Bone marrow iron

Five of the ten patients in this series underwent sternal marrow puncture twice during the study once in the pre treatment period and a *second time after 6 weeks* systemic steroid therapy Two other patients refused a second sternal puncture The results of the histochemical and chemical analyses of the marrow storage iron are shown in Table VII The tendency obtained was a removal of the hemosiderin iron from the

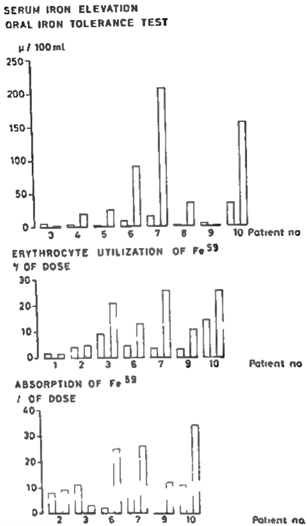


Fig 3

Iron absorption estimated with iron tolerance test erythrocyte utilization of Fe^{59} and absorption of Fe^{59} For each subject the result is indicated before (left column) and during (right colum) corticosteroid medication

bone marrow Only one patient (No 10) displayed a higher histochemical content of iron at the second puncture (during steroid treatment)

g Endogenous carbon monoxide production

This was entirely unchanged during the observation period the initial mean was 0 90 per cent S D 0 52 and after the 6

Table VII

Bone marrow iron estimated histochemically and chemically

Subject No	Histochemical estimation		Chemical estimation mg/100 g	
	Before steroid therapy	During steroid therapy	Before steroid therapy	During steroid therapy
1	++++	++		
2	+++	0		
3				
4				
5	(+)	0	16 6	7 1
6	(+)	0	7 0	5 3
7	+	0	12 6	7 1
8				
9	++	0		
10	(+)	++	32 4	28 2

weeks treatment the mean was 0 96, SD 0 57 per cent Four subjects were smokers which would account for the high mean

b Serum protein

The electrophoretic pattern did not change significantly during the observation period

The change in the patients clinical activity *during the period of treatment* was roughly parallel to the improvement or lack of improvement in the ESR

Discussion

The patients were untreated with respect *to corticosteroids they had active rheumatoid* arthritis anemia was ignored in their selection The corticosteroids or corticotrophin were given in ordinary therapeutic doses

The doses were not altered during the *trial* The observation period *of 6 weeks on* steroid therapy is too short for a study of hematological data however there was no possibility of keeping the patients to this regime for any longer They were in fact followed for 12 weeks altogether and, to judge from the fall in the ESR the therapy in general had an appreciable effect on the inflammatory process, although in no case did the ESR achieve normal values

The hematological values increased considerably but there were no changes in the erythrocyte indices This agrees with the results of Finch & al (13) and Edgcumbe & Husain (9) in arthritic subjects Agarwal (2 3) in hematologically healthy asthmatic children and Fisher (14) who reported the same findings in the rat

The *statistical* evaluation *of serum iron* concentration must be handled with great care As pointed out by Vahlquist (36) the standard deviations are large For 15 healthy men he found a standard deviation *of* 41 0 *μg/100 ml (mean* 135 5) for 15 healthy women 37 0 μg/100 ml (mean 119 5) (cf Chapter I Table X) The individual standard deviation calculated from values ob

by a hyperactive R E S (cf Gardner & Roy 16)

The resistance of the anemia of rheumatoid arthritis to orally administered iron might also be partly ascribable to a trapping of the iron absorbed from the gut in the R E S of spleen and liver Gardner & Roy (16) studied the iron storage in 34 cases of rheumatoid arthritis and 43 controls undergoing autopsy They found splenic enlargement in the rheumatoid arthritis group which together with tissue iron estimations suggested that the spleen may contain approximately twice as much iron in this disease as is normally the case These findings may be compatible with the view that iron absorbed from the gut via the portal system is trapped in the spleen (and liver) and is not utilized by the marrow for erythropoiesis

The re utilization of iron from broken down red cells is more efficient in patients with iron deficiency (about 100 per cent) than in healthy persons (about 50 per cent) according to Noyes & al (27) Haurani & al (19) showed that patients with anemia of inflammatory origin including 2 patients with rheumatoid arthritis had defective re utilization of iron This agrees with the view of Freireich & al (15) who assumed a defective release to the plasma from the reticuloendothelial tissue in patients with rheumatoid arthritis In the present patients the bone marrow hemosiderin diminished during the treatment with corticosteroids Conceivably the (anti inflammatory) effect [illegible] made good the defective iron [illegible] reticuloendothelial cells [illegible] could be used for hemat[illegible] [illegible] was achieved b[illegible] [illegible] in the number [illegible] [illegible]

is an open question Ringertz & al (8) reported destruction of the cortical rather than the medullary tissue of mouse thymus during ACTH administration Marshall (23) stated that the stem cells of lymphoid tissue (primitive reticular cells) appear unaffected by adreno cortical hormones although it is possible that a stimulatory effect occurs when these cells are involved in hemopoiesis He also reported that generalized lymph node enlargement occurs in 50—75 per cent of cases with rheumatoid arthritis with enlargement of germinal centres having numerous primitive reticular cells The spleen shows similar changes Thus in patients with rheumatoid arthritis there is probably an enlargement of the reticuloendothelial system The animal experiments of Ringertz & al (28) and Berglund & al (6) suggest that administration of corticosteroids may lead to a contraction of the R E system

Seemingly anemic patients with rheumatoid arthritis and adequate storage iron display improvement in their hematological parameters when treated with corticosteroids However no further improvement is obtained after the storage iron has been removed from the depot organs An increased iron absorption (Table VI) might compensate for these empty iron stores if enough iron is supplied in the food The report of the Empire Rheumatism Council (11) provides some suggestions in this respect In this report one group treated with corticosteroids displayed a significant elevation of the hemoglobin values at the end of the first year but the means decreased to initial levels during the 2nd and 3rd years As the patients did not receive iron therapy their storage iron was probably inadequate at the end of the trial with decreasing hemoglobin values as a result

Swanson & Bauer (35) studied the effects of steroids on oral iron loading in six hematologically normal subjects six anemic patients with rheumatoid arthritis and two with iron deficiency anemia Three of the arthritic subjects displayed higher serum iron levels when the test was repeated during corticosteroid treatment. In the present study the iron absorption has been estimated in three ways (1) oral iron tolerance test (2) absorption test with Fe^{59} and (3) determination of erythrocyte utilization of Fe^{59} 2—3 weeks after administration of the radioiron dose The number of subjects is rather limited but the results of the three tests (summarized in Table VI and Fig 3) do suggest that a real increase in iron absorption was induced by corticosteroid administration to the arthritic patients in this study

There is a practical side to these findings since the hematological values and iron absorption increase and the storage iron decreases during steroid administration it may be advisable to administer iron in conjunction with corticosteroids to anemic patients with rheumatoid arthritis The bone marrow iron should be checked during long term steroid therapy

Summary

Ten patients with active rheumatoid arthritis have been studied before and during corticosteroid treatment with respect to hematological values blood, plasma and red cell volumes iron absorption and bone marrow iron

The following changes ascribed to the corticosteroid treatment were found

Increases in hemoglobin concentration hematocrit and total iron binding capacity the erythrocyte indices remained unchanged

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The bone marrow study indicated a mobilization of the storage iron in 6 out of 7 patients

No changes were found in the blood plasma or red-cell volumes

A possible explanation for some of the findings is a retardation effected by the steroids of the hyperactive reticuloendothelial system in patients with rheumatoid arthritis

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be due to hyperactivity in the reticuloendothelial system with a defective return to the transferrin bound plasma iron pool (14). It is conceivable that the administration of corticosteroids influences this mechanism. Ebaugh (8), for instance, reports that the plasma Fe disappearance T 1/2 was prolonged when 100 mg hydrocortisone per day was administered to eight patients with rheumatoid arthritis; findings are discussed in Chap. VII which may relate to a depression of the hyperactive reticuloendothelial system (plasma cell hyperplasia) elicited by corticosteroid therapy.

Absorption of iron

Several investigators have studied the absorption of iron from the gastrointestinal tract. Using an iron tolerance test, Jeffrey (21) found a strong rise in serum iron in three cases of rheumatoid arthritis and an insignificant rise in eight. Roy & al. (45), using the same technique, found no indications of impaired absorption in patients with rheumatoid arthritis. Using an Fe^{59} technique, Jeffrey & al. (22) found that absorption was increased in arthritis patients compared with controls; our own investigations (12) with this technique showed subnormal absorption in patients with rheumatoid arthritis and similar results are reported by Roberts & al. (42, 43) and Raymond & al. (38). In the relatively large number of arthritis patients presented in Chap. II, iron absorption was studied in relation to relevant hematological data. The results were compared with those for controls and patients with iron deficiency anemia. Taken together, most of the isotope studies, including the present, indicate that patients with rheumatoid arthritis have subnormal iron absorption. A comparative study, using both fecal recovery and total body counting to measure iron absorption in a number of subjects (27), gave a correlation coefficient of 0.8 between the two methods.

Erythrocyte survival time

The Ashby technique (cross transfusion) indicates that the survival time is shortened when erythrocytes from hematologically normal donors are transfused to recipients with rheumatoid arthritis (1, 13, 28). On the other hand, the survival time was normal as a rule for erythrocytes transfused from arthritis donors to arthritis recipients (1).

A shortened survival time was demonstrated for only 4 of 50 patients with rheumatoid arthritis in a study using erythrocytes labelled with Cr^{51} (26). Using this technique on 21 patients, Richmond & al. (41) found signs of a moderately increased elimination of the labelled donor erythrocytes and concluded that there is a mild hemolytic process in patients with rheumatoid arthritis. In a similar study, Biechl & al. (3) found a shortened erythrocyte survival time in only 1 out of 20 patients with rheumatoid arthritis. Weinsten (56) reported a shortened survival time in 6 out of 13 patients, but only 2 of the cases (with splenomegaly) had values outside the 95 per cent confidence interval for normal values (cf. 3). In a study of 30 patients with active rheumatoid arthritis, Mongan & Jacox (30) transfused Cr^{51} labelled erythrocytes from either normal or rheumatoid arthritis donors. Cross-transfusion from healthy donors to arthritic recipients was studied in three pairs of identical twins, of whom only one member of each pair had rheumatoid arthritis. The survival time showed no reduction that was not ascribable to blood group incompatibility.

GENERAL DISCUSSION

Type of anemia

In both men and women with active rheumatoid arthritis, the hemoglobin concentration, red cell count and serum iron concentration were reduced compared with the controls The mean corpuscular hemoglobin (MCH) was slightly reduced for the women but remained within normal limits (Chap I) The same tendency was found for a smaller number of cases in which hematocrit and thus MCV and MCHC were also calculated (Chap II), subnormal hematocrits and MCHC being displayed by the arthritis patients A slight hypochromia has thus been found in the arthritis patients investigated in full agreement with the reports from other investigations (14 33) None of the cases displayed a macrocytic anemia of the type described by Partridge & Duthie (35) Nor have we found the more pronounced hypochromia described by Richmond & al (40) and Jeffrey (21), probably because the element of iron deficiency anemia was not so pronounced among our patients as in the English investigations No evidence of gastrointestinal hemorrhage induced by salicylicates (37 46 53 54) was found among the present patients None of them had occult blood in the feces at the time of the examinations It is noteworthy that MCH did not change with ESR or clinical activity (Chap I) This may be taken to indicate that the erythrocytes which reach the blood stream have a relatively good hemoglobinisation, although the number of erythrocytes is reduced

A further indication that the incorporation of iron is not defective in the erythrocytes which are formed in patients with rheumatoid arthritis is that the utilization of Fe^{59} in circulating erythrocytes 2—3 weeks after the oral dose was not subnormal in these patients (Chap II) The utilization of iron sorbitol given intramuscularly was not subnormal either (Chap III) Storage iron is lacking in between 14 per cent (49 own cases Chaps II III, IV) and approximately 33 per cent (29, 40) of cases It is conceivable that these are the cases which have a tendency to hypochromia and which slightly depress the mean erythrocyte indices (cf Chap II, fig 1, which shows that some of the patients had a greater rise of serum iron in the oral iron tolerance tests) The relationship between the amount of storage iron and hematological data in rheumatoid arthritis patients is being studied at present and more information may become available concerning the incidence of iron deficiency anemia in arthritis patients

Re utilization of iron from decomposed erythrocytes may thus be relevant to the degree of iron saturation in circulating erythrocytes Noyes & al (34) report that such iron is utilized to about 100 per cent in patients with iron deficiency anemia and to approximately 45 per cent in hematologically normal persons Haurani & al (19) state that the re utilization is defective in patients with inflammatory conditions two of their cases being patients with rheumatoid arthritis This impairment of re utilization may

be due to hyperactivity in the reticuloendothelial system with a defective return to the transferrin bound plasma iron pool (14). It is conceivable that the administration of corticosteroids influences this mechanism. Ebaugh (8), for instance reports that the plasma Fe disappearance T 1/2 was prolonged when 100 mg hydrocortisone per day was administered to eight patients with rheumatoid arthritis findings are discussed in Chap VII which may relate to a depression of the hyperactive reticuloendothelial system (plasma cell hyperplasia) elicited by corticosteroid therapy

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In the present study 22 women with rheumatoid arthritis had an endogenous carbon monoxide production of 0.52 per cent compared with 0.60 per cent in 18 healthy women (Chap. II). All the subjects were non smokers, a category for which the endogenous carbon monoxide is lower than in smokers (11). The endogenous production of carbon monoxide in non smoking subjects is a sensitive indicator of hemolysis (11, 18), these results thus support the more recent investigations cited above, since they indicate that hemolysis is not of decisive importance for the genesis of anemia in rheumatoid arthritis.

Hemodilution

In a study of the plasma volume with Evans blue and the red cell volume with Cr^{51} labelled autotransfused erythrocytes in 10 anemic women with rheumatoid arthritis and 10 healthy women, Dixon & al. (6, 7) found that in the arthritis group the plasma volume was increased by 20.4 per cent (significant), the blood volume was increased by 9.6 per cent (significant) and the red cell volume was numerically (but not significantly) decreased by 7.1 per cent. They considered that the findings supported Robinson's (1943) opinion that the anemia in rheumatoid arthritis is due to an increase in the plasma volume. Weinsten (56) found an augmented plasma volume in 10 out of 18 patients with active rheumatoid arthritis and concluded that in some cases the anemia could be ascribed, at least in part, to hemodilution. On the other hand, Jeffrey (21, 25) and Read & al. (39), using a similar technique, were unable to verify this increase in plasma volume in patients with rheumatoid arthritis.

The determination of total hemoglobin and blood volume by the alveolar carbon monoxide method (50) has not been reported previously for patients with rheumatoid arthritis. The method was found to be reliable and convenient; if necessary the same subject can be investigated several times in one day. Good agreement was obtained between this method and various isotope dilution techniques (iodine labelled albumin [10], iodine labelled albumin and transferrin, Chap. IV). The present study (Chap. IV) does not support the hypothesis that hemodilution is an important cause of the anemia in rheumatoid arthritis. Rheumatoid arthritis patients, who were in bed during the examination, were compared with active healthy persons. An [illegible] per cent difference in serum protein concentration has been reported between active and recumbent normal subjects, the difference being ascribed to the increase in plasma volume in persons lying in bed (24). An 8—10 per cent difference in hematocrit and serum protein concentration has been reported for changes in position (9). Fifty active patients with various diagnoses were examined for changes in hemoglobin concentration after 15 minutes in bed and it was found that the mean fell by approximately 8 per cent (Kaijser-Ekelund, personal communication). The results indicate that allowance must be made for the difference in position when comparing a group of patients in bed with a group of active controls. It is not clear whether Dixon & al. (6, 7) made a correction for this factor.

A significantly increased plasma volume in the arthritis cases was found in the largest groups compared in the present series (45 women with rheumatoid arthritis and 27 healthy women, Chap. IV). However, the

major part of the increase can be explained by the *difference in* position of the controls and the patients

Strandell (52) demonstrated a strong positive correlation between total hemoglobin and weight in healthy men. In the present study no such significant correlation was found for the normal women and nor was there a correlation between weight and blood volume red cell volume and plasma volume Thus in the normal women the amount of circulating blood (measured as total hemoglobin blood and red cell volume) did not increase with increasing weight This is probably because a higher weight is accompanied not by a greater amount of active muscle but by an increase in fatty tissue which does not have the same vascular supply as muscle (cf e g 16 31) The women with rheumatoid arthritis on the other hand showed a significant correlation between weight and total hemoglobin blood plasma and red cell volume This suggests that in these patients a higher weight corresponds to a greater amount of muscle As a rule these patients are asthenic and thus deviate from the normal female population

However when the total hemoglobin blood plasma and red cell volumes were related to body length considerably more significant correlations were obtained both for arthritic and control females the significances reached the 1 to 0 1 per cent levels this was also the case for the female controls

Anemia and changes in serum protein

The rise in various serum protein fractions has been used in several reports as a measure of the activity of rheumatoid arthritis (5 32 36 47 48 49 51) Shetlar & al (47) found that the glycoproteins were elevated in the total protein albumin pseudo globulin and mucoprotein in sera from patients with rheumatoid arthritis but not in patients with degenerative joint disease

The glycoprotein/protein quotient is correlated to the clinical activity in patients with rheumatoid arthritis (36) The serum albumin concentration showed a highly significant negative correlation with this quotient In a subsequent report clinical activity was shown to be highly significantly correlated to the serum glycoprotein concentration and c reactive protein (48) In a study of the relationship between clinical activity and the serum protein component (determined by paper electrophoresis) as well as this component s content of glycoprotein in patients with rheumatoid arthritis (51) it was found that an increasing severity of the rheumatoid process was accompanied by a rise in all the globulin fractions in particular for alpha$_2$ globulin. A corresponding significant decrease in the serum albumin fraction was demonstrated with rising disease activity The highest correlation with clinical activity of the disease was found however for the total serum glycoproteins

Bottiger & al (5) correlated the clinical activity in patients with rheumatoid arthritis with ESR the rheumatoid factor the serum concentrations of haptoglobin seromucoid protein bound carbohydrates (e g hexos hexosamin sialic acid) and the serum concentrations (determined by paper electrophoresis) of albumin alpha$_2$ and gamma globulin The laboratory findings were compared with respect to different degrees of clinical activity (48) in patients with rheumatoid arthritis and also with normal findings The results showed that the parameters investigated were not superior to ESR as an indicator of the clinical activity in rheumatoid

arthritis The system put forward by Shetlar and co workers is well documented (36, 47, 48, 49, 51) and has been used in the present study for relating laboratory data and clinical activity in patients with rheumatoid arthritis

In connection with anemia and the changes in serum proteins it is interesting that Hume & al (20) recently reported that in the treatment of anemia in rheumatoid arthritis, better results were obtained for patients with normal serum gamma globulin concentrations than in those with increased concentrations

Data reported in Chapter V suggest that there is a strong positive correlation between albumin and hemoglobin concentrations in the patients with rheumatoid arthritis The clinical activity was correlated to hematological variables and the concentrations of the various serum protein fractions, the hemoglobin concentration has been correlated to the above parameters tested by Bottiger & al (5) using the material published by them In addition to the correlation demonstrated between the concentrations of albumin in serum and hemoglobin in blood, there was a strong correlation between the total amounts of circulating albumin and total hemoglobin the latter measured by the alveolar carbon monoxide technique

Degradation of albumin and transferrin

The clear reduction of the serum albumin and transferrin concentrations in the anemia of rheumatoid arthritis (25 Chaps II V) may be due either to a decreased synthesis or to an increased decomposition, or a changed distribution The rate of synthesis of these proteins can be assessed by studying the degradation of labelled serum protein fractions in a subject in a steady state, i e with constant serum concentrations of the protein in question

The question whether the hyperglobulinemia per se depresses the albumin synthesis is still debated If the low albumin values in serum from patients with rheumatoid arthritis were due to reciprocal suppression of albumin synthesis, effected by hyperglobulinemia, one would expect a low catabolic rate of the albumin in these patients On the contrary we found the albumin catabolism to be slightly increased in the arthritic subjects Accelerated albumin degradation is found when there is pathologic albumin loss into the urine in nephrosis or into the gut in the protein losing enteropathies

Wetterfors & al (57) using ^{131} labelled albumin in man showed that there is a significant elimination of albumin via the gastric and duodeno jejunal juices, i e 4—6 g per 24 hours via the jejunum In the dog it was found that approximately two thirds of the total albumin catabolism occured in the duodenum jejunum and ileum and approximately 10 per cent in the stomach (58) A study of the distribution of extra and intravascular albumin in the dog showed that the highest values for albumin per unit tissue weight were in the gastrointestinal tract (59) In an investigation of the distribution of I^{131} labelled transferrin in two patients at autopsy 3 and 16 days respectively after the injection of this substance Awai & Brown (2) found the highest radioactivity in the thyroid gland duodenum and stomach These authors also studied the elimination of iodine labelled transferrin in five patients using in vivo buffered gastric juice in no case was more than 1 per cent of the recovered I^{131} activity found in the protein precipitable fraction indicating a

non significant elimination of transferrin via the gastric juice in these cases (four normal subjects and one patient with pernicious anemia) It remains to be seen whether the increased catabolism of transferrin and albumin in the present patients with rheumatoid arthritis is due to a possible increase in the intestinal leakage of these proteins

It is not yet known whether the hyper catabolic hypoalbuminemia that occurs in thyreotoxicosis hypercortisonism and other hypermetabolic states (fever infection) is due to an accelerated protein loss through the gut or represents a true hypercatabolism None of our patients had fever or cortisone therapy during the actual period The hypoalbuminemia in our cases could not be explained by altered distribution of body stores as the extravascular albumin pool had lower values than normal

Effect of corticosteroid therapy on the anemia in rheumatoid arthritis

Early in the corticosteroid era many studies were made on patients with rheumatoid arthritis concerning the influence of the corticosteroid therapy on bone marrow and the red and white blood cells Only a couple of reports deal with changes in the iron m abolism Swanson & al (55) found an increased rise in the serum iron concentration in an oral iron tolerance test during corticosteroid therapy studying a small material of normal cases and patients with iron deficiency anemia Ebaugh (8) examined eight patients with rheumatoid arthritis before and after treatment with 100 mg hydrocortisone per os daily for four weeks Moderate increases were demonstrated for hematocrit, red-cell volume serum iron and the intravascular iron pool as well as a significant prolongation of plasma iron disappearance T 1/2 No change was found in the utilization of Fe^{59} administered intravenously In the present series of patients who received considerably smaller doses of corticosteroids a tendency was found in certain changes in the iron metabolism in the form of increased absorption of iron from the gastrointestinal tract and mobilisation of s orage iron from the bone marrow

A moderate anemia appears in the rat 2—3 weeks after adrenalectomy (17) The same effect has been demonstrated by Gemzell & Sjostrand (15) in hypophysectomised rats Birke (4) investigated the endogenous production of corticosteroids in rheumatoid arthritis patients not receiving steroids and found that in some the excretion of 17 OH steroids in the urine was low in the normal region As a whole the values for the group were within normal limits

In the present study twenty four patients with rheumatoid arthritis but no history of corticosteroid treatment were examined for any correlation between the hemoglobin concentration and the urinary excretion per 24 hours of 17 ketosteroids and 17 hydroxisteroids No correlation was found between the degree of anemia and the excretion of these metabolites even when the latter were related to the body weight No evidence was found that an impaired endogenous production of corticosteroids in patients with rheumatoid arthritis is an important cause of the anemia in this disease

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GENERAL SUMMARY

The hemoglobin concentration and the red cell count were reduced in patients with active rheumatoid arthritis the mean corpuscular hemoglobin was decreased for both women and men, but remained within normal limits Comparisons between the hematological means and the erythrocyte sedimentation rate with the patients grouped according to disease activity (measured with clinical parameters exclusively) showed that the anemia in rheumatoid arthritis as measured by hemoglobin concentration red cell count and serum iron concentration runs parallel to clinical activity but that the mean corpuscular hemoglobin is not significantly correlated to the clinical activity or to the level of the erythrocyte sedimentation rate

The mean corpuscular hemoglobin concentration and mean corpuscular volume were reduced indicating slight hypochromia and slight microcytosis

Serum iron and transferrin concentrations were subnormal but the unbound iron binding capacity was not reduced the mean saturation percentage for a rheumatoid arthritis group lay between the means for a group of healthy controls and an iron deficient group

The endogenous carbon monoxide production was estimated to be quite normal in a rheumatoid arthritis group This negates any significantly increased breakdown of hemoglobin

The bone marrow contained histochemically demonstrable iron in 42 out of 49 patients with rheumatoid arthritis

Iron absorption measured with Fe^{59} and the fecal recovery technique was decreased $(0.05 > P > 0.01)$ in a group of female patients with rheumatoid arthritis compared with a female control group The incorporation of Fe^{59} paralleled the absorption calculated as a percentage of the absorbed dose, the utilization in the arthritic patients was of the same magnitude as in controls and in patients with iron deficiency

The utilization in circulating erythrocytes of an intramuscularly administered Fe^{59} labelled iron preparation (iron sorbitol citric acid) was the same in a group of patients with active rheumatoid arthritis as in a control group (mean 28 4 and 26 4 per cent respectively) There was no evidence of an increased incorporation of the labelled iron in the liver spleen or bone marrow in the patients with rheumatoid arthritis to judge from external radioactivity measurements over the respective organs The labelled iron sorbitol was excreted in urine to the same extent in arthritic patients and in controls (mean 33 5 and 29 6 per cent respectively)

The hypothesis that hemodilution from an increased plasma volume is a cause of the anemia in rheumatoid arthritis was tested in a comparison between patients with rheumatoid arthritis a group of iron deficiency patients and a control group using the alveolar carbon monoxide method The mean plasma volume was found to be moderately increased in the arthritic patients compared with the controls + 7 6 per cent for the females and + 5 7 per cent for the males

The difference, however, is largely ascribable to the discrepancy in the plasma volume between persons in recumbent (patients) and upright (controls) positions The study supports the conclusion that the anemia in rheumatoid arthritis is a true anemia, with reduction of hemoglobin concentration, total hemoglobin and red cell volume, hemodilution is not an important factor

Patients with rheumatoid arthritis were studied for a possible relationship between anemia, clinical activity of the disease and abnormalities in the serum proteins Correlation analysis between hematological and serum protein variables showed that the decrease in albumin concentration was of the same magnitude as the decrease in hemoglobin concentration, and that the decreases in total circulating albumin and total hemoglobin were correlated

Patients with active rheumatoid arthritis studied with transferrin and albumin labelled with radioiodine and compared with a control group, showed subnormal intravascular, extravascular and total amounts of both proteins, and especially low albumin pools The arthritic patients displayed a highly significantly increased degradation of transferrin measured as a percentage of the intravascular pool per 24 hours or quantitatively in g per 24 hours, the degradation rate of albumin in per cent per 24 hours was probably significantly increased and the absolute amount of albumin degraded per 24 hours was slightly increased

Systemic corticosteroid treatment of patients with active rheumatoid arthritis increased the hemoglobin concentration hematocrit and total iron binding capacity, the erythrocyte indices remained unchanged A tendency to increased iron absorption from the gastrointestinal tract was obtained as well as signs of mobilisation of storage iron from the bone marrow

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by

TORBJÖRN LUNDMAN

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Translated from the Swedish

by

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Tryckeri Balder AB Stockholm 1966

CONTENTS

INTRODUCTION

Background to the study

Smoking and health have become a concept that has increasingly interested the research worker and public health organizations the world over At first it was the relationship between smoking and lung diseases that excited interest, and particularly lung cancer and chronic bronchitis but more recently there has been concern about the possibility that smoking is in some measure responsible for the great increase in mortality from cardiovascular diseases noted in the last two to three decades

A careful scrutiny and evaluation of the literature in the field is reported in Smoking and Health published by the Surgeon General s Advisory Committee on Smoking and Health in the United States in 1964[146] The conclusions reached by the Committee are based mainly on the large population studies especially the prospective ones performed since 1951 The essential conclusion yielded by this research is that there is an excess mortality of about 70 per cent for cigarette smokers A small part of this difference is due to respiratory diseases such as chronic bronchitis emphysema and lung cancer[54] [57] [6] The connection between smoking and these diseases appears to be a causal one but not that between smoking and cardiovascular diseases which constitutes a major part of the observed excess mortality

Physiologic changes resulting from inhalation of tobacco smoke may be of importance The nicotine absorbed in tobacco smoking exerts acute effects on the heart, vessels and lipid metabolism after smoking 1—2 cigarettes it causes an increase in the pulse rate a slight rise in blood pressure and through catecholamine liberation an elevation of free fatty acids[92] [illegible] [135] Constriction of the peripheral vessels lowers the skin temperature[126] The effect of nicotine on the coronary vessels as observed in laboratory animals is to increase the coronary flow in man the results have been contradictory[120] It has been tentatively concluded from these acute effects that over a long period of years smoking can produce degenerative vascular alterations

There may however be quite other factors associated with smoking that are responsible for the excess mortality of smokers from cardiovascular diseases The significance of the constitution is stressed by the American Committee "If it could be shown that cigarette smokers and non smokers had significant constitutional differences apart from any differences that might be caused by smoking itself, then a possibility would exist that some predisposition of smokers to a particular disease might also be of constitutional origin and not caused by smoking 146

The importance of heredity to the pathogenesis of coronary heart disease is a much debated problem, a solution to which has been sought in family and twin studies According to the family investigations performed by Thomas[144] [145] Russek & Zohman[127] and Rose[125], coronary heart disease displays a familial aggregation The methodologic problems have been great,

however, and the part played by heredity has not been conclusively established[59]

In a Danish twin series Harvald & Hauge found the same frequency of concordance with respect to coronary occlusion for the monozygotic and the dizygotic pairs[78] For angina pectoris, in a Swedish material, however, Cederlof, Friberg & Jonsson found a higher concordance frequency for the monozygotic twins[42]

That there may be constitutional differences between smokers and non smokers has been demonstrated in morphologic studies by, among others, Seltzer, in a prospective study of the relationship between various morphologic characteristics and smoking carried out on 922 Harvard students[132] Those that were smokers 17 years later recorded consistently larger values for all the skeletal dimensions considered Differences between smokers and non smokers have also been found in a psychologic study by Heath[80]

Twin studies by Friberg Kaij, Dencker & Jonsson[66] and Fischer[63] have shown, in addition, that monozygotic twins have similar smoking habits more often than dizygotic

The relationship between smoking and cardiovascular disease is thus a many sided problem It was considered that this might be elucidated better by studying a material of monozygotic twin pairs with different smoking habits because the constitution is then kept under control In the following a report will be given of the cardiovascular and pulmonary findings in a sample of monozygotic and dizygotic adult twin pairs discordant with respect to smoking

Methods in twin studies

Ever since the 18th century twins have been used to examine the significance of genetic factors in various connections First suggested by Galton, the method was developed later by, among others von Verschuer[147] and Dahlberg[46] In this type of twin study a comparison is made of the frequency of concordance for MZ and DZ pairs, a higher frequency for the MZ pairs indicating the operation of a genetic factor

Another approach is to compare the differences between the expected and observed frequencies of coincidence The observed frequency is the ratio between the number of pairs both members of which have the trait in question and the total number of pairs observed, including those neither member of which has the trait. The expected coincidence (binomial expectance) is calculated from the prevalence in the sample For dizygotes the difference between the expected and observed coincidence frequencies is due chiefly to environmental factors and to a lesser extent to genetic ones, for monozygotic pairs, on the other hand, it is the genetic factors that are mainly responsible for the difference If the effects of environment on the MZ and DZ pairs are assumed to be equal, the difference in the coincidence frequencies for MZ and DZ will be a measure of the influence of genetic factors If dominant genes are involved, the coincidence frequency will be high also for DZ and the effect of environmental factors will be overestimated In a study of alcoholism in twin pairs Kaij used a similar method[89]

Only qualitative variables can be treated in this way the genetic dependence of continuous variables and the influence of environment on them is best studied by variance analysis This procedure has been used by Osborne & De George in extensive studies on the morphologic and blood pressure variability[113] The same method has

been used by Takkunen in an anthropometric electrocardiographic and blood pressure investigation on male twins[143]

The co-twin control method worked out by Gesell[69] is specially suitable for studies in which the constitutional factor is to be controlled Here MZ pairs are used one partner of which has been exposed to the relevant environmental factor while the other partner serves as a control. Since MZ twins have the same genetic origin there are no constitutional differences between the subjects and the controls Another way of obtaining controls is to use DZ twins of the same sex. Although the co-twin control method has many advantages it has been little used It was employed on a small scale by Glass in pharmacologic experiments [0] In clinical research the anamnestic co-twin control method has been used by Dencker on a series of twins with cranial injuries[51] The uninjured twin was used as a control and in this way the origin of the post traumatic symptoms could be found The proband method applied by Dencker has the disadvantage however that one first selects the affected partner and then seeks his co-twin

On twin series a unique way of examining the association between various measurements can be studied by cross twin analysis by which it can be ascertained whether an association between two variables is mechanical physiologic or genetic in type[113, 143] By calculating the correlation between variable I in one subject and variable II in his co-twin and vice versa, a cross twin relation is obtained

The intra subject correlation is calculated for one randomly chosen subject in each pair the MZ and DZ pairs and the men and women being treated separately The comparison between the intra subject and cross twin correlations for the MZ pairs permits of the evaluation of the relative importance of the intra subject environment upon the relationship under examination Moreover, by comparing corresponding relationships for MZ and DZ the influence of genetic and environmental factors can be ascertained by the conventional twin technique

The Twin Register

As an aid in the investigation of the effect on health of factors of environmental hygiene a twin register was set up in 1959 at the Department of Hygiene Karolinska Institute and the Department of General Hygiene the National Institute of Public Health[39] In this register are entered the like sexed twins born in Sweden between 1886 and 1925 and still alive in 1959 The register lists some 12 000 pairs 4500 of them monozygotic and 7500 dizygotic.

By means of a mailed questionnaire Cederlof Friberg Jonsson & Kaij have examined the prevalence of respiratory symptoms and angina pectoris in relation to smoking in about 10 000 twin pairs in this register[41] The smokers in the MZ pairs discordant with respect to smoking showed a definitely greater incidence of respiratory symptoms but not of angina pectoris When only one twin in each pair was used for the calculation a group was obtained in which the constitutional factors were not controlled The prevalence of angina pectoris among smokers in this group was higher The quotient of male smokers by non smokers was 1 6 The results obtained by these workers indicate the presence of constitutional differences between smokers and non smokers

The present study was performed on a

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MATERIAL

Of 247 twin pairs invited to participate 196 complete pairs (79.5 per cent) were examined. Of these pairs 92 were monozygotic and 104 dizygotic, and they ranged in age from 38 to 77 years. The distribution of the series with respect to sex, age and zygosity is given in table 1.

Time and place of the investigation

The investigation was begun in March 1963 and completed in May 1964. The examinations for the members of a pair were arranged on different days to avoid the bias that might be incurred if the smoking habits of a twin pair were known to the investigator. Most of the twins were examined at Serafimer Hospital, Stockholm, but 28 subjects residing in Gothenburg were summoned to Sahlgrenska Hospital.

The twins arrived at the respective hospitals at 08.00 and were permitted to leave between 15.00 and 16.00. Up to 4 persons were examined each day.

Criteria for selection

The twins were selected from the Twin Register according to the following principles. The twin pairs should be concordant with respect to urban/rural environment and discordant with respect to smoking habits. The smoking discordance was classed as low if the intra-pair difference was 3—10 cigarettes a day and high if it was 11 or more according to the smoking record of the Twin Register. All the monozygotes were selected at random with respect to age and sex, and then the same number of dizygotes was chosen with the same age and sex distribution. First all MZ twins with a high discordance with respect to smoking were selected with the same number of DZ, who stated that they had always been living mainly in large towns and were resident in the cities Stockholm, Gothenburg or Malmo or in the following towns of moderate size near Stockholm: Uppsala, Vasterås, Örebro, Eskilstuna, Gavle, Linkoping, Norrkoping

TABLE 1. Twin pairs distributed according to age, sex and zygosity

		Age				
		38—47	48—57	58—67	68—77	Total
Males	MZ	21	24	8	6	59
	DZ	25	24	10	1	60
Females	MZ	15	15	1	2	33
	DZ	13	22	8	1	44
Both sexes	MZ	36	39	9	8	92
	DZ	38	46	18	2	104

series of twin pairs selected from the Twin Register that were discordant with respect to smoking

Purpose of the study

The primary object of the present investigation was to examine the association between smoking and coronary heart disease by the co-twin control method Since the connection between smoking and respiratory function is most probably causal, this association was examined chiefly to verify an effect of smoking on the series Another object was to evaluate the significance of genetic factors in coronary heart disease by applying the conventional twin method The individual problems may be expressed as follows

(1) Can an association between smoking and lung function be detected when the constitutional factors are controlled?

(2) Is there any association between smoking and coronary heart disease diagnosed on the basis of a case history and electrocardiographic examinations?

(3) Does the acute elevation in blood pressure caused by smoking result in changes in blood pressure over a long period?

(4) Does the acute effect of smoking on the lipid metabolism result in changes in the levels of serum lipids over a long period?

(5) Is there a genetic factor in coronary heart disease?

TABLE 2 Non respondents distributed according to age sex and zygosity

		Age				Total
		38—47	48—57	58—67	68—77	
Males	MZ	7	2	4	0	13
	DZ	6	7	4	1	19
Females	MZ	4	3	2	1	10
	DZ	2	6	0	2	10
Both sexes	MZ	11	5	6	1	23
	DZ	8	13	4	3	28

comprised 16 pairs Four were not at the address given or had emigrated and could not be traced The remaining 12 pairs could not attend for social reasons The distribution of the non respondents with respect to sex, age and zygosity is given in table 2

There were 8 pairs one partner of which was willing to attend the examination or was examined while the other refused for other reasons than illness in 5 the latter was a smoker in 3 a non smoker

Comments

In an investigation of this type in which both members of a pair must be present if they are to be included in the sample the chance of a 100 per cent participation is small If the programme of the examination is not to deter it must be kept within reasonable bounds though without risking loss of important information. To balance these requirements is no easy matter and it is only when the material has been collected that it can be seen whether the balancing has been successful

It is known that in any population study concerned with a particular disease persons with the disease are more likely to participate than others[44] To avoid this bias the twin pairs were not informed that it was a study on the effects of smoking

A number of pairs did not participate owing to illness, but in most cases this could be classified and compared with the known smoking habit. This group probably did not affect the end result to an appreciable extent. On the other hand the prevalence of illness among the twins absent for other reasons than ill health was not known. These twins were fairly evenly distributed with respect to age and it is unlikely that they affected the representativeness of the sample

Zygosity diagnosis

The zygosity diagnosis of the pairs in the Twin Register was made by means of a number of questions with respect to similarity which were answered by the twins themselves Further zygosity checks were made on the selected pairs Since the two members of a pair were not examined at the same time it was not possible to make a direct comparison for similarity and for this reason colour photographs were taken of most of the subjects in profile and *en face*

A serologic examination of blood group

Sandviken and Katrineholm This principle of selection gave about 50 monozygotic and 50 dizygotic pairs From the pairs with low discordance with respect to smoking all the MZ and the same number of DZ were chosen who stated that they had been living mainly in Stockholm or its vicinity This group was made up to about 150 pairs with randomly selected pairs who stated that they had been living chiefly in cities and had moved to Stockholm or its neighbourhood

Comments

An attempt was thus made to keep all the environmental factors except smoking as nearly as possible the same for the two members of the pair Such factors as city residence, mode of life and air pollution, which have been considered to be in some measure responsible for cardiovascular and respiratory diseases, were the same for the two members of a pair, these being concordant as regards urban/rural environment 19 20, 75, 84, 87 95, 117, 128

From earlier studies by Friberg *et al* 66 and Fisher63 on smoking habits in twins it is known that monozygotes are more often concordant than dizygotes This was also the case in the present study and it proved extremely difficult to find enough monozygotes that were discordant with respect to smoking and concordant with respect to urban/rural environment All the monozygotes in the Twin Register satisfying the criteria of selection were summoned for the investigation

Non response

Fifty one pairs of twins (20 6 per cent) were for various reasons not available for the study Of 11 pairs one partner was examined but the other did not attend or was not examined — in one case because of illness (ulcer) in 2 for social reasons, in 5 because they did not wish and in 3 because of death

In one case the cause of death was cerebral haemorrhage It was a man of 66 a cigarette smoker and dizygotic who had suffered from hypertension and angina pectoris His co twin who also smoked though less, was found at the examination to have angina pectoris and hypertension, and post exercise electrocardiograms displayed a segmental ST depression of more than 1 mm

The cause of death in the other case was lung cancer This was a man aged 62 a cigarette smoker and dizygotic who had suffered from bronchial asthma His co-twin who also smoked though less was found at the examination to have bronchial asthma, chronic bronchitis and angina pectoris

The cause of death in the third case was gastric cancer He was a man of 59 years a dizygote and an ex smoker His co twin was a pipe and cigarette smoker and stated at the examination that he had a gastric ulcer

Seven other pairs did not attend the examination because one partner was ill The illness in one case was invalidizing rheumatoid arthritis in 3 heart disease in one gastric ulcer and in one a leg fracture in one case the disease was not known The 3 pairs in which one partner had heart disease were 2 MZ and 1 DZ. Both members of the MZ pair were smokers the ill one smoking more in one pair and less in the other pair The affected partner of the DZ pair was an ex smoker Of one MZ pair one partner had died of myocardial infarction at 62 years (ex smoker) his co-twin who was a non smoker and was not accessible had been admitted to hospital for myocardial infarction at 55 and 62 years

The largest group among the non respondents consisted of pairs one or both partners of which refused examination from unwillingness fear and the like this group

TABLE 3 *Distribution of twin pairs according to discordance/concordance with respect to smoking exposure expressed in cigarette years*

		Discordance group A		Discordance group B		Concordance
		M	*n*	M	*n*	*n*
MZ	♂	316	45	296	17	14
	♀	188	32	205	20	1
DZ	♂	384	51	347	26	9
	♀	226	38	228	36	6

the monozygotes ($n=77$) and 316 for the dizygotes ($n=89$). This group will be referred to as *discordance group A*. When the discordant pairs both of which members were smokers were eliminated there remained 99 pairs — 37 MZ and 62 DZ. This group was designated *discordance group B* and consisted of pairs one twin a cigarette smoker and the co-twin a non-smoker. The sex distribution of the various discordant groups is given in table 3. In the female DZ group there were only 2 pairs both members of which were smokers so that discordant groups A and B were practically identical. That the mean intra-pair difference was consistently lower for the female than the male pairs suggests that the women's tobacco consumption was lower.

Comments

Even if smoking is in some measure responsible for both cardiovascular and respiratory diseases, it is improbable that the same factor in the tobacco smoke is the active agent in the two groups of diseases. There are several gases and solid particles in tobacco smoke that exert an irritant effect on the lung and inhibit the ciliary movement[146]. Since, unlike cigar and pipe smokers, cigarette smokers usually inhale, there is a greater chance of a respiratory effect among the latter. Being a function of the smoking duration and the mean cigarette consumption, lifetime cigarette smoking exposure is probably one of the best measures of calculating the chronic effects of smoking on the respiratory organ.

As regards cardiovascular diseases and smoking, nicotine has, as mentioned above, a definite pharmacologic effect on the heart, vessels and lipid metabolism. When the smoke from a cigarette is inhaled about 1.5 mg of nicotine is absorbed[40, 119, 142]. If there is a chronic effect of smoking on the heart and vessels it would be expected to be dependent on the magnitude and duration of the exposure to nicotine, since cardiovascular disease develops over a long period of time. Lifetime cigarette smoking exposure is therefore probably one of the best measures also in the calculation of the chronic effects of smoking on the cardiovascular system.

was performed on all the pairs participating in the investigation The ABO and haptoglobin systems were used A more thorough serologic examination, in which the MN and Rh systems were also included was made on the pairs that were not diagnosed in the Twin Register

In the final diagnosis account was taken of the classification in the Twin Register, the blood group determination and the photographic similarity All but 2 of the 93 pairs diagnosed as MZ in the Twin Register were so classed by these methods One of the exceptions was classed as DZ on the basis of photographic and blood group, and the other, on the basis of blood group dissimilarities All 98 pairs classed as DZ in the Twin Register were so classed on the basis of the above methods, although some of them displayed photographic and blood group similarities Of the 4 pairs that were not diagnosed in the Twin Register 3 were classed as DZ on the basis of photographic and/or blood group dissimilarities The fourth pair was assigned to the MZ group according to these criteria.

Comments

The zygosity diagnosis was based chiefly on the diagnosis in the Twin Register This was made by means of a questionnaire on the similarities between the twins as children A check of the reliability of this method was carried out by Cederlof, Friberg Jonsson & Kaij on 200 randomly selected pairs[38] Compared with thorough examination on the basis of blood group serology, these authors found that the MZ diagnosis by the questionnaire method was correct in 71 out of 72 cases These results are based on the question When growing up, were you and your twin as like as two peas or of ordinary family likeness only? The results of the present investigation gave a percentage error of the same order, 2 of the 93 being wrongly diagnosed as MZ The DZ diagnosis cannot be considered reliable, in this group there were probably a few pairs that were actually monozygotic. Such errors are hard to avoid in twin studies of this type

Grading of discordance with respect to smoking

The initial selection of twin pairs was made on the basis of the Twin Register data relating to tobacco consumption As these data were no longer valid, 3 years having elapsed since they had been collected, a detailed smoking history was taken at the examination from which it was possible to calculate more accurately the tobacco consumption and hence the intra pair difference The latter presented difficulty because there were also pairs both members of which were smokers and some were mixed smokers To note only the current cigarette smoking consumption, as has been done in several earlier studies is unsatisfactory in intra pair comparisons if the smoking duration is different within the pairs The intra pair difference was therefore calculated on the principle based on lifetime exposure to cigarette smoking

The cigarette consumption of the subject was measured as the "lifetime exposure", which is the product of the mean number of cigarettes smoked a day and the number of years the subject had been smoking this gives the lifetime exposure expressed in cigarette years Counted on this basis 30 pairs were concordant with respect to cigarette consumption Some of these concordant pairs were cigar or pipe smokers The mean intra pair difference for the 166 discordant pairs was 239 cigarette years for

In most cases the respiratory symptoms were compared separately In some however they were grouped as pathologic entities this was so for asthma and pulmonary tuberculosis

Asthma — was diagnosed if according to the history the subject had received hospital treatment for asthma and typical evidence of asthma was found (chiefly sibilant rhonchi)

Pulmonary tuberculosis — was diagnosed if there were typical radiologic signs of past or current tuberculosis of the lung Minor radiologic changes such as calcified primary complex were disregarded

An *emphysema* diagnosis might also be of interest in this connection but if it is to have any validity it must be based on clinical and radiologic appearances and the results of the lung function tests Even then however the diagnosis will be unreliable and permit of no more than an intra pair comparison for respiratory symptoms and lung function tests separately

Physical examination

The conventional physical examination was supplemented by the following items

Anthropometric measurements

These included determination of the skinfold thickness skeletal length and breadth, muscular power and height and weight

The *skinfold thickness* was determined by measurements in the subscapular and in the triceps areas on the right side of the body A Harpenden skinfold caliper was used which is designed to exert a constant pressure of 10 g/sq mm of face at all openings Two measurements were performed at each site and the mean was recorded to 0 2 mm.

Skeletal length was determined by measuring the length of the radius and tibia on the right side with a steel tape Two measurements were made and the mean was recorded to the nearest 0 5 cm.

Skeletal breadth was determined by measuring the condylar breadth on the right femur and the malleolar breadth on the right lower leg by means of a spreading caliper Two measurements were made and the mean was recorded to the nearest millimetre

Muscular power was determined by measuring the isometric power in the shoulder region the shoulder thrust and shoulder pull This was performed by means of a dynamometer of the strain gauge type which was calibrated in kilogramme force (kgf) [a] The sensitivity of the instrument could be varied Three measurements were performed and the highest value was recorded to the nearest kilogramme force

Weight measured with the subject unclothed, was recorded to the nearest kilogramme

Height measured with the shoes removed was recorded to the nearest centimetre

Blood pressure measurements

The blood pressure was measured at the beginning of the examination (casual blood pressure) and after 15 minutes rest in complete quiet (basal blood pressure) The pressure was measured on the right upper arm with the subject supine an adhesive cloth sleeve measuring 35×13 cm was used The manometer was of the mercury type Korotkoff's auscultatory method was used the systolic pressure being read at the appearance of the sounds and the diastolic at disappearance At least two measurements were performed and if the values were not

[a] Equivalent to kilopond (kp)

METHODS AND PROCEDURE

Case history

The case history was taken at interviews — one sociologic and one medical

Sociologic interview

The sociologic interview, which was conducted according to a special questionnaire, was performed by students of the Department of Sociology at the University of Stockholm. Questions on civil status family conditions and urban/rural environment were put The twins were also asked about how long they had lived together, their education, occupation and jobs they had had The smoking habits were carefully noted and details were obtained on types of tobacco, daily amounts used, methods of smoking, variations in consumption and how long they had been smoking

Medical interview

The medical interview which was performed by the author comprised a general medical and a cardiovascular and respiratory part The general medical part was carried out in accordance with a special questionnaire, which included questions on earlier health, hospital treatment and medication

The cardiovascular questionnaire was that designed and tested for several years at the London School of Hygiene and Tropical Medicine [124]

The bronchitis questionnaire was that evolved by the British Medical Research Council's Committee on the Aethiology of Chronic Bronchitis [108]

Comments

For valid intra pair comparisons it was necessary that the case history questions too, be identical for the two members of a pair The diagnosis of angina pectoris with the questionnaire is based on criteria recommended by the WHO Expert Committee on Arterial Hypertension and Ischaemic Heart Disease [33], [151] In a validity test of the questionnaire, it was found by Rose that this greatly reduced the intra and inter observer variability in the diagnosis of angina pectoris It is, however probably impossible to avoid an association of false positive diagnosis if there is a high prevalence of chronic bronchitis [123]

The questionnaire was tested against a clinical diagnosis of angina pectoris based not only on the WHO criteria but also on post exercise ECG (segmental ST depressions of 0 5 mm or more) or if the exercise test could not be performed the resting ECG (pathologic Q according to the Minnesota code)

By the means of the bronchitis questionnaire different grades of coughing phlegm and dyspnoea were recorded [141] Cough 3 months in the year is termed *persistent cough* and phlegm 3 months in the year *persistent phlegm* Dyspnoea was divided into 5 grades but the results for only grade 2 or more and grade 3 or more are presented Grade 2 is breathlessness when hurrying on the level or walking up a slight gradient grade 3 denotes shortness of breath when walking at an ordinary pace on the level

In most cases the respiratory symptoms were compared separately. In some, however, they were grouped as pathologic entities: this was so for asthma and pulmonary tuberculosis.

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Skeletal length was determined by measuring the length of the radius and tibia on the right side with a steel tape. Two measurements were made and the mean was recorded to the nearest 0.5 cm.

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Height, measured with the shoes removed, was recorded to the nearest centimetre.

Blood pressure measurements

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[a] Equivalent to kilopond (kp).

identical the procedure was repeated, the lowest value then being recorded The reading was made to the nearest 5 mm.

Comments

In indirect blood pressure measurement with a cuff the results can be affected by a number of factors, the most important of which are the intra and inter observer variability The latter can be disregarded here, since all the determinations were performed by the same person (the author) Another important factor is the circumference of the arm in relation to the width and length of the cuff, and many investigators have attempted to find which cuff dimensions give the closest agreement with the pressure measured intra arterially irrespective of arm circumference

In a study with different dimensions of cuff on 53 subjects Karvonen, Telivuo & Jarvinen found a close agreement with the pressure measured intra arterially if the cuff was 40 cm long and 14 cm wide[91] The diastolic pressure measured when the sounds disappeared showed the closest agreement with the value obtained intra arterially

Laboratory tests

Blood and urine tests

Blood and urine samples were taken from the subject in the morning after 12 hours fast and thirst Immediate determinations of the E S R, serum creatinine and haemoglobin concentration were made Twenty millilitres was stored in a freeze box for later analysis of serum lipids On the urine tests for glucose and protein were performed and if these were positive the sediment was examined

Radiologic examination of heart and lungs

The heart and lungs were examined with the subject erect, and exposures were taken in two planes for calculation of the total heart volume The relative heart volume, expressed in cubic centimetres per square metre of body surface was then calculated [88, 103] The heart volume determinations were performed by an experienced radiologist (Dr A Grepe), who also examined the heart configuration and lung films In the latter scrutiny the lung parenchyma was examined first for evidence of present or old processes, and associated shrinkage The pleurae were likewise examined. Finally, the shape of the thorax was evaluated

Lung function tests

Two types of lung function tests were performed — dynamic spirometry to ascertain the airway resistance, and nitrogen washout by a multiple breath method to detect uneven ventilation

Dynamic spirometry was performed with a Bernstein spirometer[15] After the vital capacity had been determined (*VC*) a forced expiratory spirogram was recorded The forced expiratory volume for one second ($FEV_{1.0}$) and the forced expiratory vital capacity (*FVC*) were measured on the spirogram The quotient $FEV_{1.0} \times 100/FVC$ was referred to as the percentage forced expiratory volume (*FEV%*) and was calculated from the best spirogram The determinations were performed with the subject seated and the instruction was given by an experienced nurse Each test was performed 2 or 3 times with pauses for rest The calculated volumes were converted to BTPS and recorded to the nearest 0 1 litre

Nitrogen washout by the multiple breath method was performed by a procedure evolved and tested by Lundman, Orinius & Stähle whereby the mean nitrogen concentration of each expiration can be

determined directly[104] The test was carried out with the subject seated and he was allowed to get accustomed to the apparatus with a few minutes breathing of air Pure oxygen was then inspired and after mixing each expiration was analysed for the nitrogen content The test was discontinued when the nitrogen content of the expired air had fallen to 1 per cent. The mean nitrogen concentrations were corrected for tissue nitrogen and nitrogen impurity of the oxygen The amount of nitrogen washed out per expiration was plotted on semilogarithmic paper and the deviation from the ideal linearity was expressed as the percentage nitrogen washout delay (*NWOD*) as indicated by Fowler Cornish & Kety[65]

Comments

At the sociologic interview all smokers were requested not to smoke during the two to three hours before the lung function tests were performed The subject was asked whether he had complied with this request before performing the test

To test the reproducibility in dynamic spirometry 24 duplicate determinations were performed on healthy subjects — 12 men and 12 women The standard deviation for a single determination of VC was ± 0.12 litres of FVC ± 0.10 litres and of $FEV_{1.0}$ ± 0.08 litres

As regards *NWOD* the greatest difficulty of the method lies in the interpretation of the washout curve on the semilogarithmic paper large inter and intra observer variations can easily be incurred All the calculations were performed by one observer (the author) so as to minimize the inter observer variation The co-operativeness of the subject is of course, an important factor but the result is affected less than for instance dynamic spirometry by the subject's desire to perform a good test The value of the method for grading uneven ventilation is well established[28 29]

Twenty three duplicate determinations were performed on healthy subjects 12 men and 11 women The standard deviation for a single determination was ± 12 per cent units

Electrocardiographic examination

Electrocardiograms were recorded at rest before, during and after exercise. For subjects below 40 years recordings were also made during and after an 8 minute orthostatic test. The recordings after exercise were made immediately and 3 and 10 minutes after the test. The instrument was a direct recording 4 channel electrocardiograph[a] The electrocardiograms before and after exercise were recorded with the subject supine and with the following leads I II III, aVR aVF and V_1—V_6 The paper speed was 50 mm/s

Electrocardiograms during exercise were recorded with the subject seated on a mechanically braked bicycle ergometer[b]

To avoid disturbance of the registration during exercise the reference electrode was placed on the forehead and CH_2 CH_4 CH_5 were recorded[83] During exercise registrations were performed after 2 4 and 6 minutes for each load and the heart rate was calculated from the electrocardiogram. The test during exercise was usually begun at a load of 300 kgf m/min[c] in some cases 150 kgf m/min. The load was then increased in steps for each 6 minute period with the initial load until the subject was exhausted or the tracing indicated that it

[a] Mingograf 42 Elema Schonander AB Stockholm

[b] Monark-Crescentbolagen AB Stockholm

[c] Equivalent to kilopoodmeter/min (kpm/min)

TABLE 4 *Electrocardiographic code for ST J depressions*

Code number	ST junction and segment measured in leads I, II, aVR aVF V_1—V_6		
1	ST J depression ≥ 1 mm,	ST segment horizontal or sloping downward	
2	0.9—0.5	,,	
3	< 0.5,	,,	sloping downward > 0.5 mm
4	< 0.5		horizontal or sloping downward < 0.5
5	≥ 1.0		
6	0.6—0.9		

was inadvisable to raise the load further, as occurred in a few cases (arrhythmia and pronounced ST segment depression)

Comments

The electrocardiograms were interpreted by the author according to the usual criteria.[101, 102] The interpretation was codified according to the Minnesota code[23] partly modified by Astrand[9] with respect to arrhythmia and ST segment changes The ECG code for the ST segment changes is given in table 4 The interpretation was based on leads I—III aVR, aVL, aVF and V_1—V_6 The same code was used also for registrations after exercise

For the interpretation of the electrocardiograms the inter observer variations are quite large, while the intra observer variation is considerably smaller Coding 200 electrocardiograms at intervals of 2 years Astrand[10] found an extremely close agreement for the ST segment depressions according to ST code 1—3 and slightly poorer results for segmental ST changes according to ST code 4 The interpretation of the ST changes 3 minutes after exercise showed the least variations. In the coding of the present data an attempt was made to minimize the intra observer variation For instance, the author coded the whole material over a continuous period of about 3 weeks Several electrocardiograms were coded twice to check that the criteria had not changed during the period covered by the process Segmental ST depressions according to ST code 1—3 were considered to indicate silent coronary heart disease.

For various reasons a number of subjects sometimes both members of a pair, could however, not perform the exercise test, and in addition some post exercise electrocardiograms could not be evaluated as regards the ST segments owing to digitalis therapy In these cases is was deemed necessary to apply other methods to judge whether there was coronary heart disease (CHD) This diagnosis was made according to the following criteria recommended by the WHO Expert Committee on Arterial Hypertension and Ischaemic Heart Disease[21, 33]

(a) Myocardial infarction, confirmed at hospital Evidence in resting ECG of old infarction (pathologic Q according to the Minnesota code)
(b) A history of angina pectoris.
(c) Atrial flutter or fibrillation diagnosed with resting ECG at the time of the examination for which no other acceptable explanation could be found

(*d*) Hospital treatment for cardiac insufficiency for which no other acceptable explanation could be found

CHD diagnosed on the basis of criteria (*c*) and (*d*) are of course fairly unreliable since there are a number of conditions that are manifested in such a picture A diagnosis of CHD could not however be ruled out for the twins assigned to this group

Working capacity

One measure of working capacity was (W_{max})[140] calculated in the following way To the greatest load that the subject was able to sustain for 6 minutes (W_6) was added $n \times W_d/6$ kgf m min where n is the number of minutes with the final load and W_d the difference between the two greatest loads Another measure of the working capacity namely the relation between the working intensity and change in heart rate ($W_6/\Delta f$) was calculated as specified by Granath[74] Δf is the increase in heart rate from rest seated to the end of exercise at the load W_6

Comments

For some subjects the maximum working capacity as calculated in the present study was probably not identical with the true maximum working capacity since it was the subject who should decide when the maximum had been reached In an investigation on men over 60 years of age and in sound health, however Strandell found a close correlation between the maximum oxygen uptake and W_{max} calculated as above.[140]

If for various reasons the subjects discontinued the exercise test at a submaximum level an impression of the working capacity could always be obtained from $W_6/\Delta f$[74]

Statistical methods

Usual statistical methods were applied.[138] Variables of the qualitative type such as symptoms diagnoses and electrocardiographic findings were analysed in fourfold tables giving the number of concordant and discordant pairs The one tailed hypothesis that smokers had a higher frequency of positive findings was tested by Mc Nemar s test using "Tables of the Cumulative Binomial Probability Distribution [77]

The association between various quantitative variables and cigarette consumption was examined by correlation analysis between the intra pair difference for the measured parameters and the intra pair difference for cigarette consumption The latter was given a positive sign while the intra pair differences for the measured parameters were treated with their respective signs The null hypothesis that there was no correlation was tested and the level of significance was stated at the 5 per cent* 1 per cent** or 0 1 per cent level*** The mean intra pair differences for each measured variable was calculated and the null hypothesis examined with Student s t test, the level of significance being denoted as above A positive value for the mean intra pair difference signifies that on average the more exposed co-twins have higher values

To examine the effect of heredity and environment on the variables of qualitative type a comparison can be made as mentioned above (see Twin methods) between the expected and observed coincidence frequencies for MZ and DZ. The test of the difference between the observed and expected coincidence was based on the random error in the expected number of coincidences for the appropriate sample size

To examine the effect of heredity and environment on various quantitative variables

a variance analysis was performed as by Osborne & De George[113] Here, a comparison was made between the mean intra pair variance for MZ and DZ and between the intra and inter pair variances The mean intra pair variance was calculated from the expression $\Sigma X_d^2/2n$ [1] where X_d is the intra pair difference and n the number of twin pairs The mean inter pair variance was obtained from the formula $[\Sigma X_m^2 - (\Sigma X_m)^2/n]/(n-1)$ [2] where X_m is the mean for the variable within the pair and n is the number of pairs The F distribution was used to obtain the probability level, and one tailed test of significance was performed So that the intra pair and inter pair variances should be comparable in the calculation of the F ratio, the inter pair variance was multiplied by 2

In the variance analysis a comparison was also made between MZ mean intra pair variance and mean measurement error (ME) variance as calculated from duplicate determinations, the difference for a duplicate determination being inserted in the above expression for the variance [1] A significantly lower variance for the measurement error than the MZ intra pair variance was considered to indicate the reliability of the method If the MZ mean intra pair variance exceeded the ME variance the method was regarded as unreliable or the genetic variability extremely small

The presence of a large genetic component reduces the mean intra pair variance for MZ in relation to the mean intra pair variance for DZ and the F ratio will be significant

Strong environmental factors increase the MZ intra pair variance in relation to the intra pair variance for DZ and the differences are smoothed out. The environmental factors also reduce the DZ intra pair variance in relation to the inter pair variance 113

In view of the well established negative effects of smoking on the respiratory system[146] such a relationship might have been expected in the present study if the intrapair difference for tobacco consumption calculated as *lifetime cigarette smoking exposure* was high enough. The possible effect on the respiratory system might therefore serve as a measure of the degree of exposure and if this was considered to be great enough the effects of smoking on the cardiovascular system would also be elucidated.

Respiratory symptoms

The frequency and distribution of respiratory symptoms for *discordance group A* are given in table 5. The symptoms in the table are the responses obtained for the standardized bronchitis questionnaire. Most of the symptoms occurred much more often in the twins that were more exposed to cigarette smoking than in their co-twins.

Monozygotic group. — The results for the 77 MZ pairs were analysed in fourfold tables and the distribution of the pairs discordant with respect to respiratory symptoms was examined by McNemar's test. *Significantly higher frequencies* were found for the more exposed co-twins as regards "morning cough" ($P < 0.001$), "persistent cough" ($P < 0.05$) and "morning phlegm" ($P < 0.001$).

Dizygotic group. — In the 89 DZ pairs too the more exposed co-twins displayed *significantly higher frequencies* of symptoms for morning cough ($P < 0.01$), persistent cough and morning phlegm ($P < 0.05$).

Lung function

The sample is described by the means for the measured lung function parameters *NWOD*, the various *lung volumes* and $FEV_{\%}$ distributed with respect to sex and

TABLE 5. Respiratory symptoms distributed according to smoking exposure, discordance group A

Respiratory symptoms	MZ More exposed	MZ Less exposed	DZ More exposed	DZ Less exposed
Morning cough	17	5	25	12
Day cough	9	4	16	4
Persistent cough	8	3	11	6
Morning phlegm	20	9	19	12
Day phlegm	5	1	3	6
Persistent phlegm	4	3	6	5
Dyspnoea grade 2 or more	25	21	33	27
Dyspnoea grade 3 or more	6	2	5	7
Total subjects	77	77	89	89

TABLE 6 Means for the lung function parameters with respect to sex and zygosity (Based on one member of each pair)

	MZ		DZ	
	Males $n=59$	Females $n=33$	Males $n=60$	Females $n=44$
	M±S E S D	M±S E S D	M±S E S D	M±S E S D
NWOD, % units[a]	57 *(1—360)*	52 *(1—240)*	42 *(1—280)*	52 *(1—260)*
VC litres	4 3±0 1 0 8	3 4±0 1 0 7	4 6±0 1 0 9	3 1±0 1 0 7
FVC, litres	4 3±0 1 0.8	3 4±0 1 0 7	4 6±0 1 0 9	3 2±0 1 0 7
$FEV_{1\,0}$ litres	3 4±0 1 0 7	2 8±0 1 0 6	3 6±0 1 0 9	2 5±0 1 0 6
FEV%	78 2±1 0 7.8	81 3±1 4 8 0	77 4±1 2 9.2	78 9±1 1 7 2

[a] Because of marked skew distribution only the mean and range are given

zygosity (table 6) The values are based on the subject in each pair that in the Twin Register is designated twin A, and that was probably the first to be born

The results of the analyses of the correlation between the intra pair difference for cigarette consumption and the intra pair difference for the various lung function tests are given in table 7

Monozygotic group — For the 45 male pairs in *discordance group A* the mean intra pair difference for *NWOD* was positive, this suggests that the *NWOD* was higher for the more exposed co-twins but the difference from zero was not significant ($P > 0\,05$)

The 32 female MZ pairs also gave a positive mean intra pair difference, and this too, was not significant ($P > 0\,05$) Here a positive correlation was noted, which was significant at the 10 per cent level and which suggests an association between uneven ventilation and cigarette consumption

As regards *FVC* the more exposed co-twins in the male group showed a significantly lower mean ($P < 0\,05$), since the mean intra pair difference was negative For both men and women, non significant negative correlation coefficients were obtained When the male and female groups were combined the correlation became significant at the 5 per cent level ($r = -0\,272$) and the mean intra pair difference significant at the 1 per cent level ($\bar{y} = -0\,15$ litres) The association between cigarette smoking exposure and *FVC* is shown graphically in figure 1 (top)

As regards $FEV_{1\,0}$ the means for the more exposed twins were significantly lower for both men and women the correlations were also negative, but not significant ($P > 0\,05$) If the men and women were treated as a single group the negative mean intra pair difference was significant at the

TABLE 7 *Lung function tests in relation to smoking exposure*

		Males			Females		
		$\bar{y}$	±S E	r	$\bar{y}$	±S E	r
Discordance group			MONOZYGOTIC PAIRS				
A	NWOD % units	4 9	±8 6	−0 011	7 3	±7 8	0 323
	FVC, litres	−0 18*	±0 08	−0 265	−0 11	±0 07	−0 269
♂ 45	$FEV_{1\cdot0}$ litres	−0 21**	±0 07	−0 164	−0 19*	±0.07	−0 338
♀ 32	FEV%	−1 6	±1 2	0 055	−3.2	±1 6	−0 266
B	NWOD	9	±11 5	0 512*	5 5	±8 6	0 381
	FVC	−0 08	±0 14	−0 150	−0 13	±0 09	−0 251
♂ 17	$FEV_{1\cdot0}$	−0 18	±0 14	−0 295	−0 20	±0 10	−0 371
♀ 20	FEV%	−2.8	±2 3	−0 364	−3 6	±2 0	−0 406
Discordance group			DIZYGOTIC PAIRS				
A	NWOD	9 4	±6 4	0 238	11 6	±7 4	0 295
	FVC	−0 22	±0 12	−0 074	−0 04	±0 11	−0 229
♂ 51	$FEV_{1\cdot0}$	−0 25*	±0 11	0 050	−0 02	±0 11	−0 232
♀ 38	FEV %	−2 5	±1 5	0 225	0 7	±1 5	−0 134
B	NWOD	13 4	±8 5	0 582**	12 2	±7 5	0 288
	FVC	−0 19	±0 13	−0 029	−0 05	±0 11	−0.208
♂ 26	$FEV_{1\cdot0}$	−0 29*	±0 14	0 024	−0 04	±0 11	−0 211
♀ 36	FEV%	−3 6	±1 8	0 144	0 2	±1 6	−0 128

Symbols $\bar{y}$ Mean of intra pair difference; r Correlation coefficient. Null hypothesis rejected at: * 5% level; ** 1%; *** 0 1%

0 1 per cent level ($\bar{y} = -0\ 20$ litres) The relationship between cigarette smoking exposure and $FEV_{1\cdot0}$ is shown graphically in figure 1 (middle)

For *FEV%* there were also negative values for the mean intra pair differences but only when the men and women were combined was significance obtained at the 5 per cent level ($\bar{y} = -2\ 3$ per cent units)

The 17 male MZ pairs in *discordance group B* that is the pairs consisting of a cigarette smoker and a non smoker showed a positive correlation with respect to *NWOD* which was significant ($P < 0\ 05$) this indicates an association between the degree of uneven ventilation and cigarette consumption

The 20 female MZ pairs in this group likewise showed positive values though not significant ones When these pairs were combined with the males the correlation was significant at the 1 per cent level ($r = 0\ 454$) The relation between cigarette smoking exposure and *NWOD* is shown graphically in figure 2 (upper)

As regards *FVC* $FEV_{1\cdot0}$ and *FEV%* the values were consistently negative for both men and women this suggests that for all

TABLE 6 Means for the lung function parameters with respect to sex and zygosity (Based on one member of each pair)

	MZ		DZ	
	Males $n = 59$	Females $n = 33$	Males $n = 60$	Females $n = 44$
	M±S E S D	M±S E S D	M±S E S D	M±S E S D
NWOD % units[a]	57 *(1—300)*	52 *(1—240)*	42 *(1—280)*	32 *(1—260)*
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FEV%	78 2±1 0 7.8	81 3±1 4 8 0	77 4±1 2 9 2	78 9±1 1 7 2

[a] Because of marked skew distribution only the mean and range are given

zygosity (table 6) The values are based on the subject in each pair that in the Twin Register is designated twin A, and that was *probably the first to be born*

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Monozygotic group — For the 45 male pairs in *discordance group A* the mean intra pair difference for *NWOD* was positive this suggests that the *NWOD* was higher for the more exposed co-twins but the difference from zero was not significant ($P > 0\ 05$)

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As regards $FEV_{1.0}$ the means for the more exposed twins were significantly lower for both men and women the correlations were also negative but not significant ($P > 0\ 05$) If the men and women were treated as a single group the negative mean intra pair difference was significant at the

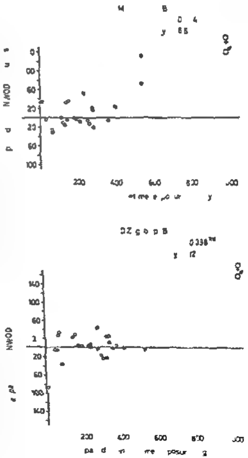
As regards dynamic sp rometry a s gnif cantly low mean was found only for $FEV_{1.0}$ in the male group In the female group the differences we e small and for $FEV\%$ even pos ti e alues were obtained for the mean intra pa r d fferences

Comments

Re p ratory symptoms

It is ev dent that there was a correlat on between prolonged cigarette smoking and the frequency of respiratory symptoms a relat onsh p that has already been well es tablished n a number of tud es Of these ment on may be made of the population study by H gg ns on 700 men in South Wales and Scotland, in wh ch smokers reco ded symptoms such as p rs stent ough and phlegm s gnif cantly more often than non smokers [81 82] Compar son of these results w th those obta ned in a sim lar study by Olsen & G lson on a sample of Dan sh men showed a lower prevalence of respiratory symptoms n the Dan h sample th s was ascr bed to d fferences n the tobacco consumpt on between these two groups [112] In 1965 H iht reported the results of a large nvest gation of a F nn sh populat on consist ng of 730 men and 890 women conducted to ascerta n the pre alence of resp ratory symptoms [85] He used the same standard zed bronch t s quest on na re that the present n estigat on and he too confirmed the close correlat on between cigarette smoking and the pre alence of resp ratory symptoms In both H gg ns and Huht s stud es the resp ratory symptoms were related to the amount of current cigarette smoking and their stud es therefore g e no nformat on on the effect of chronic c garette smok ng exposure As n the present study Andersson & Ferris found on an unselected sample in Berl n, U S A that the respiratory symptoms were also correlated w th lifet me cigarette smoking exposure [8] Thus the durat on of smok ng hab t and the number of cigarettes consumed are probably ch efly respons ble for the higher frequency of symptoms

The extremely close agreement between the results obtain d by other workers and those of the present investigation indicates that the cigarette smoking expo ure of the twin sample was on a s gn f cant level



F gu e 2 Correlation between smoking exposure and NWOD for MZ (upper) and for DZ (lower) disco dance group B

these parameters they were lower for the smoking co-twins. The values are not significant at the 5 per cent level, but since the tendency was the same for both sexes they could be treated as a single group. 5 per cent significance was then obtained for the mean intra-pair differences as regards $FEV_{1.0}$ ($\bar{y}=-0.19$ litres) and $FEV\%$ ($\bar{y}=-3.2$ per cent units) and for the correlation with $FEV\%$ ($r=-0.348$).

Dizygotic group. — For the male DZ pairs in *discordance group A* both the mean intra-pair difference and the correlation for *NII OD* were positive, though not significant ($P > 0.05$). When this and the female group (38 pairs) were combined, which was permissible because they displayed the same tendency, a 5 per cent significance was obtained for the correlation ($r=0.238$).

As regards dynamic spirometry the means for the male group were consistently lower for the more exposed co-twins, but significant only for $FEV_{1.0}$ ($P < 0.05$). The large range of the intra-pair differences for $FEV_{1.0}$ is shown in figure 1 (bottom).

In the male *discordance group B* there was a closer correlation between cigarette consumption and the degree of uneven ventilation ($P < 0.01$). When a group was formed from the 26 male and 36 female pairs, significance at the 5 per cent level was obtained for the mean intra-pair difference as regards *NII OD* ($\bar{y}=12.7$ per cent units) and at the 1 per cent level for the correlation coefficient ($r=0.398$). The relation between cigarette smoking exposure and *NII OD* is shown graphically in figure 2 (lower).

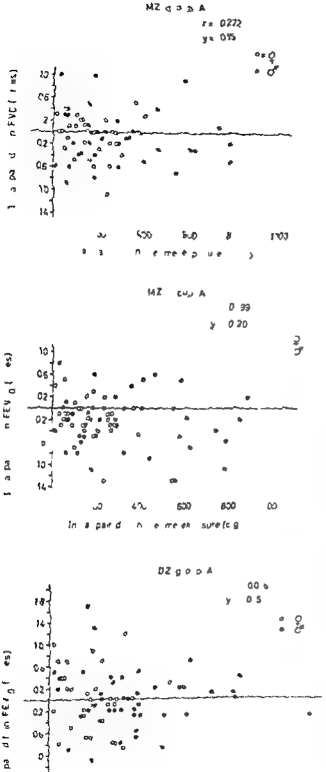


Figure 1. Correlation between smoking exposure and FVC for MZ (top), $FEV_{1.0}$ for MZ (middle) and $FEV_{1.0}$ for DZ (bottom) discordance group A.

As regards dynamic spirometry a significantly low mean was found only for $FEV_{1.0}$ in the male group In the female group the differences were small and for $FEV\%$ even positive values were obtained for the mean intra pair differences

Comments

Respiratory symptoms

It is evident that there was a correlation between prolonged cigarette smoking and the frequency of respiratory symptoms a relationship that has already been well established in a number of studies Of these mention may be made of the population study by Higgins on 700 men in South Wales and Scotland, in which smokers recorded symptoms such as persistent cough and phlegm significantly more often than non smokers [81] [82] Comparison of these results with those obtained in a similar study by Olsen & Gilson on a sample of Danish men showed a lower prevalence of respiratory symptoms in the Danish sample this was ascribed to differences in the tobacco consumption between these two groups [112] In 1965 Huhti reported the results of a large investigation of a Finnish population consisting of 730 men and 890 women conducted to ascertain the prevalence of respiratory symptoms [85] He used the same standardized bronchitis questionnaire as that in the present investigation and he too confirmed the close correlation between cigarette smoking and the prevalence of respiratory symptoms In both Higgins and Huhti s studies the respiratory symptoms were related to the amount of current cigarette smoking and their studies therefore give no information on the effect of chronic cigarette smoking exposure As in the present study Andersson & Ferris found on an unselected sample in Berlin U S A that the respiratory symptoms were also correlated with lifetime cigarette smoking exposure [8] Thus the duration of smoking habit and the number of cigarettes consumed are probably chiefly responsible for the higher frequency of symptoms

The extremely close agreement between the results obtained by other workers and those of the present investigation indicates that the cigarette smoking exposure of the twin sample was on a significant level

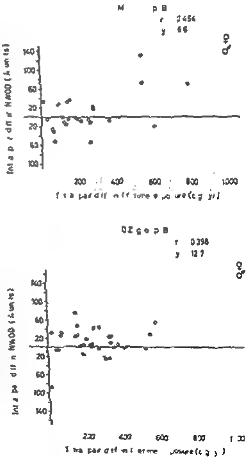


Figure 2 Correlation between smoking exposure and NWOD for MZ (upper) and for DZ (lower) discordance group B

Lung function

The relationship between cigarette smoking and the degree of uneven ventilation and the airway resistance was clearly demonstrated on the MZ pairs that were homogeneous from the constitutional aspect, it was most evident from the results for discordance group B. The unreliability in the calculation of lifetime exposure was partly eliminated in the effect study on this group.

Most of the lung function examinations that have been performed earlier on smokers have been the determination of $FEV_{1.0}$ or maximum breathing capacity (MBC), to obtain a measure of the airway resistance, and in some cases lung volume determinations have also been carried out. In a number of studies the differences between smokers and non-smokers in respect of $FEV_{1.0}$ or $FEV\%$ have been extremely small,[8, 73] while other authors especially Wilson, Meador, Joy & Higgins[152] found quite large differences. In Huhti's investigation on a Finnish population a lower $FEV_{1.0}$ was found for the male smokers but there was no correlation with the number of cigarettes consumed.[85] However, Andersson & Ferris found a weak negative relationship between $FEV_{1.0}$ and the number of cigarettes currently smoked.[8] They do not report the results for the correlation between lifetime cigarette smoking exposure and $FEV_{1.0}$.

Studies on lung function in women are few. In Huhti's investigation on a Finnish population the female smokers had higher values for $FEV_{1.0}$ and FVC than non-smokers, from which he concluded that either cigarette smoking probably does not affect the lung function of women or that the female cigarette smokers constitute a selected group.[85] That the latter is the correct conclusion is indicated by the absence of any sex difference in the present study, cigarette smoking probably affects the lung function of women to the same extent as that of men.

The effect of cigarette smoking on the lung volumes VC and FVC differs widely from one study to another. Huhti[85] and Goldsmith, Hechter, Perkins & Borhani[73] found no difference in this respect between smokers and non-smokers. In the present study, however, significant differences were recorded for the monozygotic group, while the results for the dizygotic group were not so convincing. The various lung volumes are greatly dependent on the physical constitution, especially skeletal build, and the differences between the dizygotic twins in this respect resulted in large variations in the intra-pair differences, quite apart from the influence of environment. One way of avoiding these sources of errors is to use the nitrogen washout method, which is not dependent on physical constitutional factors. This method has been used to only a small extent in earlier studies on cigarette smokers. In the combined population study by Olsen & Gilson in which nitrogen washout by the single-breath method was used on the Danish sample significantly higher values were found for the cigarette smokers.[112]

Asthma and tuberculosis, which have been said not to be associated with smoking[146] were in the present investigation uniformly distributed and therefore did not produce bias in the results of lung function. The same applies to the radiologic findings (table 8).

There are however other sources of error in the evaluation of the chronic effect of cigarette smoking on lung function that must be taken into account. Smoking of 1—3 cigarettes produces an acute airway

TABLE 8 Radiographic lung alternations distributed according to smoking exposure dis cordance group A

Chest radiography	MZ		DZ	
	More exposed	Less exposed	More exposed	Less exposed
Minor parenchymal changes without shrinking	10	14	10	8
Minor parenchymal changes with shrinking	2	3	3	4
Major parenchymal changes with shrinking	1	2	2	2
Pleural changes without shrinking	12	15	12	9
Pleural changes with shrinking	1	—	2	2
Emphysema	2	1	1	—
Thoracal asymmetry	—	1	3	2
Thoracal deformity	—	—	1	2
Total subjects	77	77	[illegible]	89

resistance which persists for 10—80 minutes[110] That this is slight has been shown by Simonson by measuring $FEV_{1.0}$ it resulted in a drop of about 0 03 litres in healthy subjects and 0 12 litres in cases of pulmonary diseases *FVC* showed no significant decrease[136] The mildness of the acute effect has been shown also in compliance studies by Damoiseau, Petit, Troquet & Pirnay[47] This source of error was eliminated from the present study, however as the smokers were required not to smoke for about three hours prior to the lung function examination

In relation to smoking

To be able to evaluate the results of the study of the relation between smoking and cardiovascular disease it was necessary that the intra pair difference in lifetime cigarette smoking exposure be large enough. That this was the case is evident from the conclusive evidence that for the co-twins more exposed to cigarette smoking there were clear signs of a higher degree of uneven ventilation and greater airway resistance.

The parameters to be treated here are weight, skinfold thickness, blood pressure, a number of symptoms and physical findings related to cardiovascular disease and electrocardiographic findings, mainly post exercise ST segment changes.

Weight and skinfold thickness

The twin sample is described by the means for some of the measured anthropometric parameters, distributed according to

TABLE 9. Means for age at examination, age at separation and anthropometric parameters with respect to sex and zygosity. (Based on one member of each pair)

	MZ		DZ	
	Males $n=59$	Females $n=33$	Males $n=60$	Females $n=44$
	M±S.E. S.D.	M±S.E. S.D.	M±S.E. S.D.	M±S.E. S.D.
Age, years	51.6±1.3 9.7	48.9±1.5 8.5	50.0±1.0 8.0	51.3±1.3 8.4
Age at separation, years	24.8±0.8 5.8	23.3±1.6 9.0	23.6±1.0 7.3	24.6±1.5 9.9
Height, cm	172.2±0.8 6.3	163.1±1.1 6.3	175.0±0.9 7.4	162.7±0.9 6.1
Weight, kg	72.7±1.3 10.1	60.3±1.9 11.0	73.9±1.5 11.7	64.3±1.7 11.3
Skinfold, triceps area, mm	9.1±0.4 2.9	15.9±1.0 5.8	8.8±0.4 3.1	18.3±0.8 5.5
Bimalleolar breadth, mm	76.5±0.5 3.5	67.7±0.6 3.2	76.9±0.5 3.7	69.0±0.6 3.7
Shoulder thrust, kgf	46.4±1.9 14.2	21.5±0.9 5.4	46.2±2.0 15.3	23.4±1.0 6.7
Heart volume, cc/m² BSA	408±10 78	338±7 40	392±7 55	350±8 52

TABLE 10 Weight and skinfold thickness in relation to smoking exposure

		Males			Females		
		$\bar{y}$	±S E	r	$\bar{y}$	±S E.	r
Discordance group				MONOZYGOTIC PAIRS			
A ♂ 45	Weight, kg	—1 5	±0 8	—0 091	—1 4	±1 7	—0 161
♀ 32	Skinfold, triceps area, mm	—0 7	±0 5	0 126	—0 7	±1 0	—0 258
B ♂ 17	Weight	—2 4	±1 5	—0 134	—3 1	±2 4	—0 017
♀ 0	Skinfold triceps area	—1 0	±1 0	0 259	—1 8	±1 1	0 151
Discordance group				DIZYGOTIC PAIRS			
A ♂ 51	Weight	—1 6	±1 7	—0 009	—3 2	±2 3	—0 150
♀ 38	Skinfold triceps area	—0 1	±0 5	0 120	—1 3	±0 7	—0 181
[illegible] ♂ 26	Weight	—4 2	±2 3	—0 067	—1 6	±1 9	—0 3 8*
♀ 36	Skinfold triceps area	—0 5	±1 5	—0 100	—0 4	±1 3	—0 315

Symbols as for table 7

sex and zygosity (table 9) The values are based on one subject in each pair Many of the parameters especially the height and skeletal measurements are chiefly genetically dependent as shown by Osborne & De George[113] and Takkunen [143] The variance analysis on the present series showed agreement in this respect but as regards the variability of weight and skinfold thickness the effect of both genetic and environmental factors was evident For this reason only the relationship between the latter anthropometric variables and cigarette consumption will be reported

The results of the correlation analyses of the intra pair difference for cigarette consumption with the intra pair difference for weight and skinfold thickness in the triceps area are given in table 10

Monozygotic group — For the 45 male MZ pairs in *discordance group A* a negative mean intra pair difference was obtained for weight this suggests that the weight was on average lower for the more exposed co-twins The value was significant at the 10 per cent level. For skinfold thickness in the triceps area, too the mean was lower for the more exposed co-twins but not significantly so (P > 0 05) The 32 female MZ pairs also showed negative values for the mean intra pair difference in weight and skinfold thickness but here it was due mainly to an extremely large difference for a single pair the non smoking partner was inactive owing to defective healing of a fracture of the femoral neck.

In neither the female nor male group was there any correlation between the loss of weight and cigarette consumption since the correlation coefficients were not significant. In *discordance group B* too the relative reduction in weight for smokers was

In relation to smoking

To be able to evaluate the results of the study of the relation between smoking and cardiovascular disease it was necessary that the intra pair difference in lifetime cigarette smoking exposure be large enough. That this was the case is evident from the conclusive evidence that for the co-twins more exposed to cigarette smoking there were clear signs of a higher degree of uneven ventilation and greater airway resistance.

The parameters to be treated here are weight, skinfold thickness, blood pressure, a number of symptoms and physical findings related to cardiovascular disease and electrocardiographic findings, mainly post exercise ST segment changes.

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The twin sample is described by the means for some of the measured anthropometric parameters, distributed according to

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	MZ		DZ	
	Males $n=59$ M±S.E. S.D.	Females $n=33$ M±S.E. S.D.	Males $n=60$ M±S.E. S.D.	Females $n=44$ M±S.E. S.D.
Age, years	51.6±1.3 9.7	48.9±1.5 8.5	50.0±1.0 8.0	51.3±1.3 8.4
Age at separation, years	24.8±0.8 5.8	23.3±1.6 9.0	23.6±1.0 7.3	24.6±1.5 9.9
Height, cm	172.2±0.8 6.3	163.1±1.1 6.3	175.0±0.9 7.4	162.7±0.9 6.1
Weight, kg	72.7±1.3 10.1	60.3±1.9 11.0	73.9±1.5 11.7	64.3±1.7 11.3
Skinfold, triceps area, mm	9.1±0.4 2.9	15.9±1.0 5.8	8.8±0.4 3.1	18.3±0.8 5.5
Bimalleolar breadth, mm	76.5±0.5 3.5	67.7±0.6 3.2	76.9±0.5 3.7	69.0±0.6 3.7
Shoulder thrust, kgf	46.4±1.9 14.2	21.5±0.9 5.4	46.2±2.0 15.3	23.4±1.0 6.7
Heart volume, cc/m² BSA	408±10 78	338±7 40	392±7 55	350±8 52

TABLE 10 Weight and skinfold thickness in relation to smoking exposure

		Males			Females		
		$\bar{y}$	±S E	*r*	$\bar{y}$	±S E	*r*
Discordance group			MONOZYGOTIC PAIRS				
A							
♂ 45	Weight, kg	−1.5	±0.8	−0.091	−1.4	±1.7	−0.161
♀ 32	Skinfold, triceps area, mm	−0.7	±0.5	0.1[illegible]6	−0.7	±1.0	−0.258
B							
♂ 17	Weight	−2.4	±1.5	−0.134	−3.1	±2.4	−0.017
♀ 20	Skinfold, triceps area	−1.0	±1.0	0.259	−1.8	±1.1	0.151
Discordance group			DIZYGOTIC PAIRS				
A							
♂ 51	Weight	−1.6	±1.7	−0.009	−3.2	±2.3	−0.150
♀ 38	Skinfold, triceps area	−0.1	±0.5	0.120	−1.3	±0.7	−0.181
B							
♂ [illegible]6	Weight	−4.2	±2.3	−0.067	−1.6	±1.9	−0.328*
♀ 36	Skinfold, triceps area	−0.5	±1.5	−0.100	−0.4	±1.3	−0.315

Symbols as for table 7

sex and zygosity (table 9). The values are based on one subject in each pair. Many of the parameters, especially the height and skeletal measurements, are chiefly genetically dependent, as shown by Osborne & De George[115] and Takkunen[143]. The variance analysis on the present series showed agreement in this respect, but as regards the variability of weight and skinfold thickness the effect of both genetic and environmental factors was evident. For this reason only the relationship between the latter anthropometric variables and cigarette consumption will be reported.

The results of the correlation analyses of the intra-pair difference for cigarette consumption with the intra-pair difference for weight and skinfold thickness in the triceps area are given in table 10.

Monozygotic group. — For the 45 male MZ pairs in *discordance group A* a negative mean intra-pair difference was obtained for weight; this suggests that the weight was on average lower for the more exposed co-twins. The value was significant at the 10 per cent level. For skinfold thickness in the triceps area, too, the mean was lower for the more exposed co-twins, but not significantly so ($P > 0.05$). The 32 female MZ pairs also showed negative values for the mean intra-pair difference in weight and skinfold thickness, but here it was due mainly to an extremely large difference for a single pair; the non-smoking partner was inactive owing to defective healing of a fracture of the femoral neck.

In neither the female nor male group was there any correlation between the loss of weight and cigarette consumption, since the correlation coefficients were not significant. In *discordance group B*, too, the relative reduction in weight for smokers was

quite moderate As figure 3 (upper) shows, the null hypothesis is not directly acceptable in the male group

Dizygotic group — In the DZ group there was a consistent tendency for the more exposed co-twins to have on average lower values for weight and skinfold thickness in the triceps area (table 10) For the 26 male pairs in *discordance group B* the mean intra pair difference in weight was significant at the 10 per cent level, and for the 36 female pairs a significant negative correlation was noted ($P < 0.05$), this indicates a correlation between the weight loss and the cigarette consumption (figure 3 (lower))

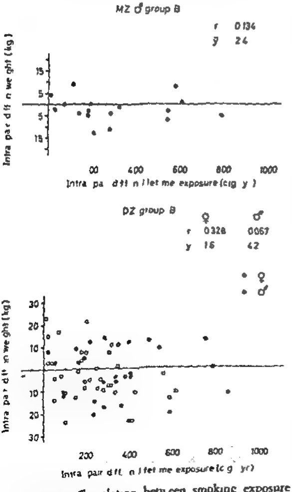

Figure 3 Correlation between smoking exposure and weight for MZ, men (upper) and for DZ (lower) discordance group B

Comments

For the male and female pairs, irrespective of zygosity, the negative values for the mean intra pair difference in weight were associated with negative values for skinfold thickness Hence, since a reduction in weight can be due to a reduction in muscle and/or skeletal mass, this showed that the slightly lower weight of the smokers was probably due to a reduction in the subcutaneous fat That there was an association between cigarette smoking and these variables is perhaps most clearly evident from the fact that the respective values became more strongly negative in the comparison between discordance group A and B

The slightly closer association between weight and cigarette consumption in the DZ group suggests that the difference in weight between the smokers and non smokers was in some measure due to constitutional factors However, the fact that there was a correlation though a weak one between these variables in the MZ group indicates that the smoking factor is of importance

That smokers weigh less than non smokers has been shown earlier In Damon s investigation on 174 men the subscapular skinfold thickness as well as the weight were less [48] Karvonen, Orma, Keys Fidanza & Brozek likewise found in a Finnish population that the smokers were slightly lower in weight, but they could not rule out the possibility that this was due to constitutional differences between the two groups [90]

The loss of weight has been ascribed to the change in diet resulting from loss of appetite caused by smoking [146] Support for this has been found in the tendency for smokers that give up smoking to put on weight [13] The loss of weight could be due

TABLE 11 Mean basal systolic and diastolic pressures and pulse rate with respect to sex and zygosity (Based on one member of each pair)

	MZ		DZ	
	Males $n=59$	Females $n=33$	Males $n=60$	Females $n=44$
	M±S.E. S.D.	M±S.E. S.D.	M±S.E. S.D.	M±S.E. S.D.
Systolic basal mm Hg	127.0±2.3 *17.6*	122.6±2.6 *15.1*	130.3±3.3 *24.5*	131.7±3.2 *21.2*
Diastolic	77.8±1.4 *10.7*	72.4±1.7 *9.9*	78.7±1.9 *14.4*	76.8±1.7 *11.4*
Pulse rate beats/min	70.2±1.3 *10.2*	71.3±1.2 *6.8*	70.1±1.5 *11.3*	71.5±1.3 *8.9*

to a higher basal metabolism among smokers for Blackburn, Brozek & Taylor found in 223 middle aged men that the basal oxygen uptake was slightly higher for smokers than non smokers 24

Blood pressure

As an analysis of the results showed that the casual blood pressure was affected to a greater extent by the examination environment, the subsequent analysis of the associa

TABLE 12 Basal blood pressure in relation to smoking exposure

		Males			Females		
		$\bar{y}$	±S.E.	r	$\bar{y}$	±S.E.	r
Discordance group		MONOZYGOTIC PAIRS					
A	Systolic basal mm Hg	−6.1*	±2.6	−0.101	−1.6	±1.8	0.131
♂ 45	Diastolic basal mm Hg	−1.9	±1.6	0.083	−0.3	±1.4	−0.007
♀ 32	Pulse rate beats/min	1.5	±1.4	0.124	0.6	±1.8	0.130
B	Systolic basal	−9.1	±5.0	−0.168	−1.8	±2.6	0.176
♂ 17	Diastolic basal	−7.6**	±2.4	−0.093	−0.5	±2.0	0.037
♀ 20	Pulse rate	0.6	±2.1	0.072	0.3	±2.6	0.091
Discordance group		DIZYGOTIC PAIRS					
A	Systolic basal	−2.1	±3.5	0.255	−3.4	±3.1	0.232
♂ 51	Diastolic basal	−2.5	±2.1	0.231	−2.9	±1.8	0.267
♀ 38	Pulse rate	−0.6	±2.2	0.056	−0.9	±2.0	−0.067
B	Systolic basal	−1.3	±5.4	0.218	−3.5	±3.2	0.202
♂ 26	Diastolic basal	−1.9	±3.0	0.028	−2.5	±1.8	0.226
♀ 36	Pulse rate	−5.5*	±2.4	0.070	−1.7	±2.0	−0.052

Symbols as for table 7

tion with cigarette consumption presented below was based only on the basal blood pressure The full range of blood pressure is considered first, and then those cases with elevated diastolic blood pressure

(a) Full range of blood pressure

The sample is described by the means for the basal systolic and diastolic pressures and the pulse rate with respect to sex and zygosity (table 11) The values are based on one subject in each pair

The results of the correlation analysis of

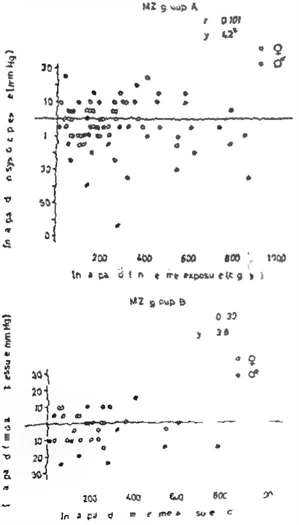

Figure 4 Correlation between smoking exposure and systolic pressure for MZ, discordance group A (upper) and diastolic pressure for MZ discordance group B (lower)

the intra pair differences for the above variables with the intra pair difference for cigarette consumption are given in table 12

Monozygotic group — For the 45 male MZ pairs in *discordance group A* a negative mean intra pair difference was obtained for both systolic and diastolic pressures this indicates that the more exposed co-twins had lower blood pressure The value for the systolic pressure was significant at the 5 per cent level ($\bar{y} = -6.1$ mm Hg)

For the 32 female MZ pairs a similar tendency was observed, but the values were not significant In neither the male nor female groups was there a correlation between cigarette consumption and blood pressure (Figure 4 (upper) systolic pressure)

The corresponding results for *discordance group B* underline the tendency for a lower blood pressure in the more exposed co-twins especially as regards the diastolic pressure in the male group whose mean intra pair difference was significant at the 1 per cent level ($\bar{y} = -7.6$ mm Hg) (Figure 4 (lower) diastolic pressure)

Dizygotic group — For the 51 male and 38 female DZ pairs in *discordance group A* negative intra pair differences were obtained in respect of the systolic and diastolic pressure this indicates that the pressure was lower for the more exposed co-twins but the range was too great for significance to be achieved The same applies to the pairs in *discordance group B*

(b) Elevated diastolic blood pressure

The relation between cigarette consumption and elevated diastolic pressures is given in table 13 (fourfold table)

Monozygotic group — If the limit between "elevated" and "normal" is put at the 95 mm level this group contained 2 concordant and 5 discordant pairs Four out

TABLE 13 Frequency of concordance and discordance with respect to elevated diastolic pressure in relation to smoking exposure discordance group A

		MORE EXPOSED					
		MZ			DZ		
		a	*b*	total	*a*	*b*	total
	a	3	6	9	10	6	16
	b	3	65	68	[illegible]	64	73
	total	6	71	77	19	70	89
LESS EXPOSED		*c*	*d*	total	*c*	*d*	total
	c	2	3	5	2	4	6
	d	1	71	72	6	77	83
	total	3	74	77	8	81	89

a ≥ 90 mm Hg *c* ≥ 95 mm Hg
b ≤ 85 *d* ≤ 90

of there 5 pairs with elevated diastolic pressure were less exposed co-twins Although the elevated level was reduced to 90 mm Hg there were fewer more exposed co-twins with elevated diastolic pressure

Dizygotic group — In this group the reverse was the case, a higher number of the more exposed co-twins recording elevated diastolic pressure the differences were however not significant ($P > 0.05$)

Comments

There was a consistent tendency for lower systolic and diastolic pressures for the more exposed co-twins in the MZ group at the time of the examination The causality is underlined by the fact that the differences were greater when the calculations were performed on discordance group B It is also evident that prolonged cigarette smoking does not cause a persistent elevation of the diastolic blood pressure

It should be borne in mind however that the blood pressure measurements on the smoking twins in this study were performed after several hours abstinence It is probable that if the nicotine concentration in the blood is kept constant the pressures recorded by smokers will be much the same as for non smokers

In the DZ group, too there was a clear tendency for a lower blood pressure in the smokers but the large range for the intra pair differences undoubtedly due to constitutional dissimilarities presented an insignificant mean difference from zero Such constitutional differences between smokers and non smokers may be the reason that not all workers have found significant differences Karvonen *et al* however found significantly lower blood pressures among smokers in a Finnish population[90] In Bronte Stewart s study[30] on 600 healthy men the observed lower value was not significant and Blackburn *et al*[25] obtained a significant lower level only for some of the male groups examined They also found that the reaction to the cold pressor test

was less marked for smokers than non smokers Furthermore, there were more hypertensive subjects among the non smokers

Cardiovascular history and some physical findings

The distribution of some of the more important case history and physical findings in relation to smoking is given in table 14 for MZ and DZ, *discordance group A*

Monozygotic group — The prevalence of diagnoses such as myocardial infarction intermittent claudication and diabetes mellitus was low and there was no difference in this respect between the more and less exposed co-twins The differences as regards *angina pectoris* were negligible irrespective of whether this was diagnosed by means of the questionnaire or clinically" Nor were the nontypical symptom *chest pain or discomfort* and *arcus lipoides corneae*, the prevalence of which was high, more common among the smokers

Dizygotic group — The prevalence of the various cardiovascular findings and diagnoses was the same in the DZ and MZ groups, and the distribution was largely the same except for the *chest pain or discomfort* which for DZ was more common (but not significantly so) among the more exposed co twins

Comments

No relationship was found between smoking and cardiovascular symptoms and diagnoses in the MZ group, but the prevalence of most of these conditions was too low to permit of definitive conclusions The prevalence of arcus lipoides corneae, which has been found to be more common in arteriosclerotics of middle age[1, 139] was lower, but it, too, was not more common among the smokers

In the DZ group there was evidence of an association between non characteristic chest pains and smoking, but these can as well be of respiratory origin and cannot be considered as a symptom of CHD That the respiratory symptoms can result in false positive diagnosis of angina pectoris when the questionnaire is used has been pointed

TABLE 14 Cardiovascular symptoms and diagnoses distributed according to smoking exposure discordance group A

	MZ		DZ	
	More exposed	Less exposed	More exposed	Less exposed
Chest pain or discomfort	28	34	30	22
Angina pectoris questionnaire diagnosis	4	2	4	5
doubtful	2	[illegible]	2	2
clinical diagnosis	4	2	3	5
Myocardial infarction	1	—	1	3
Intermittent claudication	—	—	1	1
Diabetes mellitus	2	1	1	1
Xanthelasma	—	2	3	2
Arcus lipoides corneae	19	18	13	15
Total subjects	77	77	89	89

TABLE 15 Mean W_{max} $W_d/\Delta f$ heart rate and respiration rate at end of exercise test with respect to sex and zygosity (Based on one member of each pair)

	MZ		DZ	
	Males $n=57$	Females $n=31$	Males $n=60$	Females $n=42$
	M±S E. S D	M±S E. S D	M±S E S D	M±S E S D
W_{max} kgf m/min	783±29 2.0	519±24 135	846±28 219	514±22 142
$W_d/\Delta f$ kgf m/min pulse beat	10 3±1 3 3.2	7 3±0 6 3.4	11 1±0 6 4.5	7.2±0 4 2 3
Final heart rate beats/min	158±2 6 19 3	157±2 9 16.8	157±2 3 17 9	153±2 6 16 9
Final breathing rate breaths/min	25±0 7 5 1	26±0.8 4 3	28±0 6 4.8	26±0 9 5 7

out by Rose,[123] it may be one of the reasons for the more frequent diagnoses of this condition made on the basis of the cardiovascular questionnaire than by clinical examination in the present study (diagnosed in 19 and 11 twin pairs, respectively) As mentioned above for this diagnosis the pain history in accordance with the WHO criteria should be supplemented with segmental ST depressions of 0 5 mm or more in the post exercise ECG or if an exercise test could not be performed a pathologic resting ECG (in 2 cases pathologic Q according to the Minnesota code) Of the 9 subjects classed as having "clinical angina pectoris and who performed an exercise test, 2 had angina like pains and 1 chest pains during the test In 8 subjects the clinical and questionnaire diagnoses were identical The other 11 subjects who according to the questionnaire had angina pectoris had normal resting and post exercise ECGs

It is a familiar fact that angina pectoris is a fairly uncommon condition among persons with *CHD* It is not certain that the members of a twin pair with equally advanced CHD have this symptom. On small samples this symptom does not provide an adequate measure of the prevalence of CHD and other more sensitive methods must be relied upon

Physical working capacity

The exercise test was performed mainly to obtain an electrocardiographic record in connection with physical exercise and only secondarily to measure the working capacity It has been shown by Blomquist that the magnitude of ST segment changes in connection with exercise are linear up to 60 per cent of the aerobic capacity and they become more marked if the maximum or near maximum load is used[26] The intra pair comparison with respect to working capacity — that is the connection between this and cigarette consumption — treated in the following will therefore be of extremely great importance for the intra pair comparison with respect to post exercise ST segment changes

As a description of the sample the means or W_{max} $W_d/\Delta f$ pulse and respiratory rate

at the end of the exercise test are given in table 15 for the MZ and DZ, men and women The values are based on one subject in each pair

The results of the correlation analyses of the intra pair differences for the above parameters with the intra pair difference for cigarette consumption are presented in table 16

Monozygotic group — For the 43 male MZ pairs in *discordance group A* the mean intra pair difference and the correlation with respect to W_{max} and $W_0/\Delta f$ were negative, this suggests that there was a negative association between working capacity and cigarette consumption Although the mean intra pair difference for W_{max} was significantly negative ($P < 0.05$) the difference from zero was small (50 kgf m/min) in relation to the absolute mean load (about 800 kgf m/min)

At the end of the exercise test the more exposed co twins had on average a non significantly lower heart rate At the same time their respiratory rate was slightly higher

The results for the 30 female MZ pairs were the same as those for the men as regards $W_0/\Delta f$ and respiratory rate The weak association between cigarette consumption and W_{max} is shown in figure 5

The corresponding analysis for the males

TABLE 16 Working capacity in relation to smoking exposure

		Males			Females		
		$\bar{y}$	±S E	r	$\bar{y}$	±S E	r
Discordance group		MONOZYGOTIC PAIRS					
A	W_{max} kgf m/min	−50*	±25	−0.239	37	±22	−0.146
♂ 43	$W_0/\Delta f$ kgf m/min/pulse beat	−0.21	±0.33	−0.255	−0.27	±0.61	−0.275
♀ 30	Final heart rate beats/min	−3.3	±2.0	0.185	−0.6	±2.7	−0.025
	Final breathing rate breaths/min	1.0	±1.0	−0.074	1.2	±0.8	0.384*
B	W_{max}	−57	±42	−0.724**	21	±32	−0.077
♂ 15	$W_0/\Delta f$	0.40	±0.51	−0.569*	−0.47	±0.89	−0.322
♀ 19	Final heart rate	−6.9*	±1.7	−0.221	−2.1	±3.7	0.095
	Final breathing rate	0.6	±1.7	0.159	1.3	±1.1	0.544*
Discordance group		DIZYGOTIC PAIRS					
A	W_{max}	−42	±35	−0.127	−15	±29	−0.112
♂ 49	$W_0/\Delta f$	−0.53	±0.50	0.286	0.66	±0.44	0.384*
♀ 36	Final heart rate	−1.6	±2.8	−0.240	−5.4	±3.4	−0.196
	Final breathing rate	2.5*	±0.9	−0.326*	0.1	±1.1	0.300
B	W_{max}	−75*	±36	0.114	−8	±30	−0.155
♂ 26	$W_0/\Delta f$	−1.68*	±0.63	0.404*	0.83	±0.46	0.352*
♀ 34	Final heart rate	2.1	±3.3	−0.155	−7.3*	±3.3	−0.200
	Final breathing rate	2.5	±1.2	−0.209	0.4	±1.1	0.263

Symbols as for table 7

of *discordance group B* showed a significantly *negative* correlation in respect of both W_{max} and $W_{g}/\Delta f$, while the mean intra pair differences did not differ significantly from zero. The correlation for W_{max} was at least to some extent false, since the *final heart rate for the more exposed co-twins* was significantly lower.

The more exposed co-twins in the female group showed a non-significant negative mean intra-pair difference and correlation *for $W_{g}/\Delta f$ and significantly positive correlation* for respiratory rate at the end of the exercise test.

Dizygotic group. — For the 49 male pairs in *discordance group A* the mean intra-pair differences for W_{max} and $W_{g}/\Delta f$ were negative but not significant. On the other hand the more exposed co-twins had a significantly higher respiratory rate at the end of the exercise.

In the female group there was no difference between the more and less exposed co-twins as regards W_{max}, but a significant positive correlation was found for $W_{g}/\Delta f$; this suggests that the more exposed co-twins had a higher working capacity.

A corresponding analysis for *discordance group B underlined the tendency detected in discordance group A*.

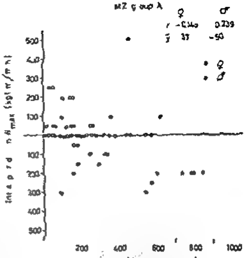

Figure 5. Correlation between smoking exposure and W_{max} for MZ, discordance group A.

Comments

In the present investigation the correlation between W_{max} and smoking was weak; this may have been due to the subjects not achieving their true maximum working capacity. *The mean heart rate at the end of the exercise for the various age groups of men and women of the whole series was* compared with Astrand's results[11] for the maximum heart rate obtained for healthy male heavy workers of the corresponding age groups; as is seen from figure 6, in none

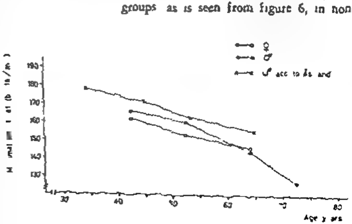

Figure 6. Comparison between maximum heart rate for the present material and Astrand's results for male labourers[11].

TABLE 17 Electrocardiographic changes at rest distributed according to smoking exposure discordance group A

ECG changes at rest	MZ More exposed	MZ Less exposed	DZ More exposed	DZ Less exposed
Arrhythmias				
Bigeminal or trigeminal ventricular ectopic beats (VEB)	—	1	—	—
Frequent (4 or more in 40 complexes) VEB and supra ventricular ectopic beats (SVEB)	—	1	—	—
Frequent VEB	1	—	—	—
Frequent SVEB	—	—	1	—
Occasional (less than 4 in 40 complexes) VEB	—	1	2	1
Occasional SVEB	2	1	—	—
Atrial fibrillation	—	—	1	—
Q wave pathologic	1	—	—	2
ST segment				
ST code 1	—	—	1	—
2	1	2	1	3
3	2	—	1	1
4	—	3	2	—
5	—	—	—	—
6	1	—	—	2
T wave				
≧ −5 mm	—	—	1	1
−1 to −5 mm	—	—	1	3
Flat or diphasic	—	1	3	1
Low amplitude	3	1	2	3
Digitalis therapy	3	1	1	1
Total subjects	77	77	89	89

of the age groups in the present study were these maximum levels achieved Although the differences were not significant this shows that the values for W_{max} obtained in the present series were presumably only submaximal

The fact that the more exposed co-twins consistently recorded a slightly lower final heart rate during exercise indicates that the load they managed was restricted by other factors than the heart rate It is a familiar fact that smokers have an elevated carboxy haemoglobin concentration, which ranges from 4 to 10 per cent [146] For constant haemoglobin concentration the oxygen capacity is therefore decreased [43, 98, 99] and this means that the expected maximum working capacity for smokers should be slightly lower An intra pair comparison with respect to the subjective complaints given for discontinuing the exercise test disclosed no difference Nor was there any difference between the more or less exposed co-twins as regards heart volume or haemoglobin concentration The observed negative intra pair differences as regards W_{max} and

TABLE 18 Electrocardiographic changes 3 minutes after exercise distributed according to smoking exposure, discordance group A

ECG changes 3 min after exercise	MZ		DZ	
	More exposed	Less exposed	More exposed	Less exposed
Arrhythmias				
Bigeminal or trigeminal ventricular ectopic beats (VEB)	—	1	—	—
Frequent (4 or more in 40 complexes) VEB and supra ventricular ectopic beats (SVEB)	—	—	—	—
Frequent VEB	1	—	1	—
Frequent SVEB	—	—	1	—
Occasional (less than 4 in 40 complexes) VEB	1	1	1	—
Occasional SVEB	—	1	—	—
Atrial fibrillation	—	—	—	—
Q wave pathologic	—	—	—	2
ST segment				
ST code 1	2	4	5	6
2	7	12	10	13
3	1	1	4	—
4	5	11	8	14
5	2	1	—	—
6	9	11	11	9
T wave				
≧ − 5 mm	1	—	1	1
− 1 to − 5 mm	—	1	2	4
Flat or diphasic	1	—	3	1
Low amplitude	5	[illegible]	7	8
Exercise test not performed	2	3	2	1
Digitalis therapy	2	1	[illegible]	1
Total subjects	77	77	89	89

final heart rate might however have been due to respiratory discomfort, since the lung function of the more exposed co twins was found to be significantly affected Evidence that this is the case is found in the *consistently higher respiratory rate at the* end of the exercise test

The relation between the load and the increase in heart rate ($W_d/\Delta f$) at submaximal level may however be considered as a measure of the circulatory adaptation[74] and it is evident from the present results that there was a weak association between cigarette consumption and this quantity The divergent results as regards $W_d/\Delta f$, at least for the female mono- and dizygotes suggests that the smokers and non smokers *may be constitutionally dissimilar*

Electrocardiographic findings

The distribution of certain ECG changes registered at rest and 3 minutes after exercise for MZ and DZ, *discordance group A* are presented in tables 17 and 18

TABLE 19 Frequency of concordance and discordance with respect to post exercise ST segment depressions, in relation to smoking exposure MZ, discordance group A

	MORE EXPOSED					
	Males			Females		
	a	*b*	total	*a*	*b*	total
a	5	5	10	7	10	17
b	0	33	33	0	12	12
total	5	38	43	7	22	29
LESS EXPOSED	*c*	*d*	total	*c*	*d*	total
c	3	5	8	3	5	8
d	0	35	35	3	18	21
total	3	40	43	6	23	29

a ST code 1—4 *c* ST code 1—3
b ST code 0 or 5—6 *d* ST code 0 or 4—6

ST segments in these tables does not include ST segment changes due to digitalis therapy If ST T changes were noted in the orthostatic test on subjects less than 40 years old and the same type of changes were found also in post exercise ECGs, it was considered that the ST T changes were most probably of the sympatheticotonic type and are therefore not reported under ST segment in table 18 This was the case for 4 subjects and the ST change was of the ST code 4 type

In the resting ECGs the frequency of ST segment changes, as of other pathologic findings, was low, and since the reliability of this test in the diagnosis of silent CHD is known to be low a more thorough analysis was limited to the segmental ST depressions in the post exercise ECG

The relationship between these ST changes and cigarette consumption is evident from tables 19 and 20, which show the concordance and discordance frequencies for segmental ST depressions of various degrees 3 minutes after exercise for *discordance group A*

Monozygotic group — Of the 43 male pairs where both co-twins had evaluable post exercise ECGs there were 5 concordant pairs and 5 discordant, if ST code 1—4 was regarded as a unit In these 5 discordant pairs it was always the less exposed co twin that recorded the ST changes Among the 29 female MZ pairs segmental ST depressions were also more common for the less exposed co twins

Even when only segmental ST depressions of at least 0 5 mm were considered the less exposed co-twins displayed the higher frequency

Dizygotic group — Of the 46 male DZ pairs 12 were discordant as regards ST code 1—4 (table 20) The distribution among the more and less exposed co-twins was the same The distribution was not appreciably altered in either the male or female group if only ST code 1—3 changes were considered

TABLE 10 Frequency of concordance and discordance with respect to post exercise ST segment depressions in relation to smoking exposure DZ discordance group A

	MORE EXPOSED					
	Males			Females		
	a	*b*	total	*a*	*b*	total
a	4	6	10	11	11	22
b	6	30	36	5	10	15
total	10	36	46	16	21	37
LESS EXPOSED	*c*	*d*	total	*c*	*d*	total
c	2	4	6	5	7	12
d	5	35	40	6	19	25
total	7	39	46	11	26	37

a ST code 1—4 *c* ST code 1—3
b ST code 0 or 5—6 *d* ST code 0 or 4—6

Technical discards

Out of the whole twin sample there were 17 twins whose post exercise ECGs could not be judged owing to digitalis medication or because the exercise test could not be carried out owing to pathologic resting ECG or disabilities

These 17 twins belonged to 15 pairs which thus constituted the total loss due to unacceptable post exercise ECG and for which no intra pair comparison could be made as regards the post exercise ST changes Of these 8 were MZ and 7 DZ. Since 4 of the pairs were concordant with respect to smoking the loss in *discordance group A* was 11 pairs (5 MZ and 6 DZ) The above 17 twins were judged from the aspect of CHD by other methods than the exercise test (criteria see Methods, p 18) Eight of these were diagnosed as CHD Two died a few months after the examination and the clinical diagnosis of CHD was confirmed at autopsy A female MZ pair belonging to *discordance group A* was concordant with respect to the clinical CHD diagnosis The 5 MZ pairs in *discordance group A constituting the technical* loss due to unacceptable post exercise ECG included 3 subjects with a clinical diagnosis of CHD and 2 with ST segment depressions according to ST code 1—3 after exercise If these ST changes are combined with the clinical diagnosis of CHD 2 pairs were concordant and 1 pair discordant It was in this case the less exposed co-twin that was healthy

The 6 DZ pairs in *discordance group A* constituting the technical loss of pairs due to unacceptable post exercise ECG included 2 subjects with a clinical diagnosis of CHD and 2 with segmental ST depressions according to ST code 1—3 after exercise Even when the segmental ST depressions are combined with the clinical diagnosis of CHD there was no concordant pair the 4 subjects all belonging to different pairs Two were non smokers and 2 smokers.

It is evident from this that the relation

TABLE 19 Frequency of concordance and discordance with respect to post exercise ST segment depressions, in relation to smoking exposure, MZ, discordance group A

	MORE EXPOSED					
	Males			Females		
	a	*b*	total	*a*	*b*	total
a	5	5	10	7	10	17
b	0	33	33	0	12	12
total	5	38	43	7	22	29
LESS EXPOSED	*c*	*d*	total	*c*	*d*	total
c	3	5	8	3	5	8
d	0	35	35	3	18	21
total	3	40	43	6	23	29

a ST code 1—4 *c* ST code 1—3
b ST code 0 or 5—6 *d* ST code 0 or 4—6

"ST segments" in these tables does not include ST segment changes due to digitalis therapy If ST T changes were noted in the orthostatic test on subjects less than 40 years old and the same type of changes were found also in post exercise ECGs, it was considered that the ST T changes were most probably of the sympatheticotonic type and are therefore not reported under ST segment in table 18 This was the case for 4 subjects and the ST change was of the ST code 4 type

In the resting ECGs the frequency of ST segment changes, as of other pathologic findings, was low, and since the reliability of this test in the diagnosis of silent CHD, is known to be low a more thorough analysis was limited to the segmental ST depressions in the post exercise ECG

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Even when only segmental ST depressions of at least 0 5 mm were considered the less exposed co-twins displayed the higher frequency

Dizygotic group — Of the 46 male DZ pairs 12 were discordant as regards ST code 1—4 (table 20) The distribution among the more and less exposed co-twins was the same The distribution was not appreciably altered in either the male or female group if only ST code 1—3 changes were considered

significance[10] Depression of ST J without a change in form of the ST segment occurs more often after exercise tests where the heart rate has reached high values[137] and is probably not a sign of coronary insufficiency as has been pointed out by Robb & Marks[122]

It was found by Blomquist that the ST segment depressions were more marked at the end of exercise than afterwards[26] For technical reasons however electrocardiographic registrations during exercise are difficult to classify, so that in the present study it was chosen to evaluate only post exercise changes In the evaluation of these changes however account should be taken of the fact that the ECG picture is often influenced to a greater extent by sympathetic tone after than during exercise[67] According to von Ahn tobacco smoking results in a flattening of the T waves and slight depression of the ST segments owing to an increase in sympathetic tone and heart rate[5] This effect is of relatively short duration and as the smokers in the present study had not smoked prior to the exercise test this error was eliminated

In order to be able to make intra pair comparisons of the post exercise ST changes it was thus important that the cardiac effort or the relative load for the two subjects of a pair should be about equal A rough measure of the relative load is provided by the heart rate attained during the exercise test As was found from the intra pair comparison the more exposed co-twins had discontinued the test at a slightly lower heart rate a difference that ranged from 0 6 to 7 6 beats min in the monozygote group was negligible at the absolute heart rate in question (110—190 beats min) This difference in heart rate can however partly explain why the more exposed co-twins less frequently recorded ST segment depressions after exercise.

The twins that did not perform the exercise test owing to pathologic ECG or whose ECG could not be evaluated as regards the ST segment owing to digitalis medication were responsible for a technical loss of 11 pairs many of whom were in bad health Although the subjects with a clinical diagnosis of CHD are combined with the cases with segmental ST depressions in the post-exercise ECG there was still no association with cigarette consumption. These results suggest that smoking is not a significant factor in the causation of coronary heart disease

Genetic considerations

The conclusion that smoking is not an important factor in the pathogenesis of coronary heart disease lends support to the suspicion expressed by the Surgeon General s Advisory Committee on Smoking and Health that the association between smoking and CHD found by other authors might not be causal but perhaps of constitutional origin[146] Only if coronary heart disease is found to have a genetic component, however can constitutional differences between smokers and non smokers be regarded as responsible for the excess morbidity and mortality found among smokers An attempt was therefore made to ascertain the relative significance of environmental and genetic factors to coronary heart disease and to examine the association between various cardiovascular parameters The whole twin sample (196 pairs) was used, including the smoking concordant pairs

Coronary heart disease

(a) Clinically manifest disease

Table 22 presents the prevalence and the

TABLE 21 Frequency of concordance and discordance with respect to post exercise ST segment depressions, combined with clinical CHD diagnosis if the post exercise electrocardiogram could not be assessed in relation to smoking exposure, MZ and DZ, discordance group B

		EXPOSED					
		MZ			DZ		
		a	*b*	total	*a*	*b*	total
NOT EXPOSED	*a*	4	6	10	4	11	15
	b	3	24	27	9	38	47
	total	7	30	37	13	49	62

a ST code 1—3 or CHD clinical diagnosis
b ST code 0 or 4—6 or no CHD

ship between the more and less exposed co twins is not appreciably altered if account is taken of the results for these 11 pairs constituting the technical loss

If account is taken of the technical discards in discordance group B and the presence of segmental ST depressions after exercise are combined with the clinical diagnosis of CHD positive findings were in these cases, too, not more common among the more exposed co-twins (table 21)

Comments

Most of the diagnostic methods available for detecting CHD are fairly unreliable [131] Resting ECGs often show a normal picture even when CHD has been established by clinical examination, and silent conditions will usually remain undiagnosed by this method [16, 105] Silent CHD may be detected by evaluating electrocardiograms in association with exercise As has been shown by Mattingly [107] and Robb & Marks [122] coronary insufficiency is related to the segmental ST depressions in the post exercise ECG In Master s double two step test only a moderate effort is expended and a negative test therefore does not rule out CHD At a follow up of 800 patients, however, Master & Rosenfeld found that only 3 per cent of those recording a negative test developed CHD [106]

The magnitude and frequency of ST segment depressions in connection with exercise is directly dependent on the relative load, as has been shown by Blomquist,[26] and the number of false negative tests should be less if a maximal or submaximal load is chosen, but then a number of false positive tests may be obtained It was concluded by Doan Peterson, Blackmon & Bruce who examined ECG changes in 433 asymptomatic men after maximum exercise that this test was more sensitive than Master s double two step test for detecting coronary insufficiency [52] In the present study horizontal or downward sloping ST segments with a depression of at least 0 5 mm (ST code 1—3) were considered to indicate silent coronary heart disease It has been shown by Astrand that in submaximal load one should also note the horizontal ST segment changes with a depression less than 0 5 mm (ST code 4) since at a follow up study these proved to be of some prognostic

significance.[10] Depression of ST J without a change in form of the ST segment occurs more often after exercise tests where the heart rate has reached high values [137] and is probably not a sign of coronary insufficiency as has been pointed out by Robb & Marks [122]

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Coronary heart disease

(a) Clinically manifest disease

Table 22 presents the prevalence and the

TABLE 22 Prevalence and expected and observed coincidence frequencies for angina pectoris, diagnosed on the basis of the questionnaire, and overt CHD (n, number of pairs)

		Prevalence	Expected coincidence		Observed coincidence	
		%	*n*	%	*n*	%
MZ	Angina pectoris,					
$n=92$	questionnaire diagnosis	4.4	0	0.2	2	2.2
	CHD clinical diagnosis	3.8	0	0.1	2	2.2
DZ	Angina pectoris,					
$n=104$	questionnaire diagnosis	5.8	0	0.3	0	0
	CHD, clinical diagnosis	5.3	0	0.3	1	1.0

expected and observed coincidence frequency for *angina pectoris* diagnosed on the basis of the cardiovascular questionnaire and for *clinically manifest CHD* according to the WHO criteria. As is seen from the table, the prevalence was too low to permit of any statistical testing regarding the observed differences between the expected and observed coincidence frequencies

Table 23 presents the results for the corresponding calculations relating to *arcus lipoides corneae* About one third of the MZ twins had this symptom and as many as 20 pairs were concordant The observed coincidence frequency therefore exceeded the expected at a high level of significance ($P < 0.001$)

The prevalence, as the observed coincidence frequency for the 104 DZ pairs, was lower than for the MZ pairs, and the difference from the expected coincidence frequency was not significant ($P > 0.05$) Although there is no suitable statistical test for evaluating the difference between the MZ and DZ groups, the values suggest that arcus lipoides corneae is greatly dependent on genetic factors

(b) Silent coronary heart disease

Table 24 shows the prevalence and the expected and observed coincidence frequencies for the segmental ST depressions after exercise according to ST code 1—4

For the 84 MZ pairs where post exercise ECGs could be evaluated for both co-twins

TABLE 23 Prevalence and expected and observed coincidence frequencies for arcus lipoides corneae (n number of pairs)

	Prevalence	Expected coincidence		Observed coincidence		
	%	*n*	%	*n*	%	*P*
MZ $n=92$	27.2	7	7.4	20	21.7	< 0.001
DZ $n=104$	16.8	3	2.8	6	5.8	> 0.05

TABLE 24 *Prevalence and expected and observed coincidence frequencies for various grades of post exercise ST segment depressions (n number of pairs)*

	ST code	Prevalence %	Expected coincidence n	Expected coincidence %	Observed coincidence n	Observed coincidence %	P
MZ	1—4	28.0	7	7.8	14	16.7	< 0.01
n = 84	1—3	16.1	2	2.6	6	7.1	< 0.05
	1—2	14.9	2	2.2	5	6.0	< 0.05
	1	3.0	0	0.1	0	0	—
DZ	1—4	35.6	12	12.7	19	19.6	< 0.05
n = 97	1—3	23.7	5	5.6	10	10.3	< 0.05
	1—2	21.6	5	4.7	9	9.3	< 0.05
	1	7.2	0	0.5	2	2.0	—

there was a significantly higher observed coincidence frequency than was expected for all grades of ST segment depressions according to the ST code

The values for the 97 DZ pairs are largely in agreement with those for the monozygotic group that is to say there was a significantly higher observed than expected coincidence frequency

As has been pointed out above the technical loss due to unacceptable post exercise ECGs was 15 pairs (8 MZ and 7 DZ) In these pairs 13 subjects performed an exercise test with a valid ECG These displayed segmental ST depressions in post exercise ECG according to ST code 1 in 1 case, ST code 2 in 4 and ST code 4 in 2 cases Of the other 17 technical discards 8 had a clinical diagnosis of CHD

If the clinical diagnosis of CHD in these cases is combined with the post exercise ST depressions according to code 1—3 then 3 of the 8 MZ pairs were concordant Of the 7 DZ pairs none was concordant

Table 25 gives the prevalence and the expected and observed coincidence frequencies regarding post exercise ST depressions of various grades combined with the 8 subjects with a clinical diagnosis of CHD and numbered among the technical loss

The prevalence in the MZ group increased from 16.0 to 19.0 per cent if the group with segmental ST depressions according to ST code 1—3 and a clinical diagnosis of CHD are considered The observed coincidence frequency showed a relatively greater increase and the differences between the expected and observed were significant at the 1 per cent level

The 104 DZ pairs also displayed a higher coincidence frequency than expected but the difference between this and the observed frequency was not significant ($P > 0.05$) The difference between the MZ and DZ groups would seem to be real and to indicate the presence of a strong genetic component but in the absence of a suitable method it could not be established statistically

Comments

The prevalence of manifest CHD — that

TABLE 22 Prevalence and expected and observed coincidence frequencies for angina pectoris, diagnosed on the basis of the questionnaire, and overt CHD (n, number of pairs)

		Prevalence	Expected coincidence		Observed coincidence	
		%	*n*	%	*n*	%
MZ	Angina pectoris,					
n = 92	questionnaire diagnosis	4 4	0	0 2	2	2 2
	CHD clinical diagnosis	3 8	0	0 1	2	[illegible] 2
DZ	Angina pectoris,					
n = 104	questionnaire diagnosis	5 8	0	0 3	0	0
	CHD clinical diagnosis	*3 3*	*0*	*0 3*	*1*	*1 0*

expected and observed coincidence frequency for *angina pectoris* diagnosed on the basis of the cardiovascular questionnaire and for *clinically manifest CHD* according to the WHO criteria. As is seen from the table, the prevalence was too low to permit of any statistical testing regarding the observed differences between the expected and observed coincidence frequencies

Table 23 presents the results for the corresponding calculations relating to *arcus lipoides corneae* About one third of the MZ twins had this symptom and as many as 20 pairs were concordant The observed coincidence frequency therefore exceeded the expected at a high level of significance ($P < 0\ 001$)

The prevalence, as the observed coincidence frequency for the 104 DZ pairs, was lower than for the MZ pairs, and the difference from the expected coincidence frequency was not significant ($P > 0\ 05$) Although there is no suitable statistical test for evaluating the difference between the MZ and DZ groups, the values suggest that arcus lipoides corneae is greatly dependent on genetic factors

(b) Silent coronary heart disease

Table 24 shows the prevalence and the expected and observed coincidence frequencies for the segmental ST depressions after exercise according to ST code 1—4

For the 84 MZ pairs where post exercise ECGs could be evaluated for both co-twins

TABLE 23 Prevalence and expected and observed coincidence frequencies for arcus lipoides corneae (n number of pairs)

	Prevalence	Expected coincidence		Observed coincidence		
	%	*n*	%	*n*	%	*P*
MZ *n* = 92	27 2	7	7 4	20	21 7	$< 0\ 001$
DZ *n* = 104	16 8	3	2 8	6	5 8	$> 0\ 05$

frequency than expected. The importance of genetic components in coronary heart disease would however have been under estimated unless account had been taken of the technical loss due to unacceptable ECGs One half of this group of subjects consisted of cases of overt coronary heart disease and if there is a strong hereditary factor, these would be expected to include a higher pro portion of concordant MZ than DZ pairs This was in fact the case and when the whole sample was considered the MZ group showed a higher level of significance be tween the expected and observed coinci dence frequencies for segmental ST depres sions of at least 0 5 mm combined with the clinical diagnosis of coronary heart disease The fact that in the DZ group this was not the case indicates that the genetic component in coronary heart disease is fairly strong

The findings of the present investigation are in agreement with those of earlier fa mily studies Comparing the incidence of CHD and the parental history of CHD in students at the Johns Hopkins School of Medicine Thomas found that among those having a parental heredity there was a higher frequency of CHD [144, 145] Rose found a similar tendency in 75 CHD pa tients with matched controls [125] Inter racial studies have yielded slightly discrepant re sults but there is abundant evidence that the observed differences are of genetic origin [100]

The results for arcus lipoides corneae constitute indirect support for the presence of a genetic component in coronary heart disease since in persons of middle age there is an association between them [139]

Blood pressure

(a) Variability of blood pressure

Systolic blood pressure (table 26) — The F ratios for the DZ and MZ intra pair variances were significant. A high level of significance was obtained for the F ratios between the inter and intra pair variances for both MZ and DZ. This shows that the variability of the systolic blood pressure is greatly influenced by genetic factors The corresponding F ratios for the female group showed a higher level of significance than the male

TABLE 26 Basal systolic pressure mean variances

	Male				Female			
	n	Variance	*F*	*P*	*n*	Variance	*F*	*P*
MZ_{ia}	59	188.4			33	51.5		
DZ_{ia} MZ_{ia}			1.59	< 0.05			4.68	< 0.001
DZ_{ia}	60	297.9			44	240.9		
DZ_{ir} DZ_{ia}			2.46	< 0.001			4.32	< 0.001
DZ_{ir}	60	366.1			44	545.4		
MZ_{ir} MZ_{ia}			3.70	< 0.001			8.48	< 0.001
MZ_{ir}	59	300.4			33	220.9		

Symbols *ia* intra pair
ir inter pair

TABLE 25 Prevalence and expected and observed coincidence frequencies for various grades of post exercise ST segment depressions, combined with clinical CHD diagnosis if the post exercise electrocardiogram could not be assessed (n, number of pairs)

		Prevalence	Expected coincidence		Observed coincidence		P
		%	n	%	n	%	
MZ n = 92	ST code 1—4 or CHD[a]	31 0	9	9 6	17	18 5	< 0 01
	1—3 or CHD[a]	19 0	3	3 6	9	9 8	< 0 01
DZ n = 104	ST code 1—4 or CHD[a]	35 6	12	12 7	19	18 3	> 0 05
	1—3 or CHD[a]	24 5	6	6 0	10	9 6	> 0 05

[a] Clinical diagnosis

is angina pectoris and myocardial infarction — in a middle aged population is about 4—6 per cent[61] Because of this low figure it is difficult to assess the significance of heredity in CHD, particularly from family studies[59, 60] In the population investigation in Tecumseh comprising 8000 persons with a prevalence of CHD of about 5 5 per cent no familial aggregation was evident[61]

With the twin method too it is difficult to make a confident statement although large samples are examined In the Danish twin series consisting of about 7000 pairs Harvald & Hauge did not find a higher concordance frequency for MZ twins than for DZ twins as regards "coronary occlusion"[78, 79] In a mailed questionnaire study on 5877 pairs aged 38 to 77 years however, Cederlof, Friberg & Jonsson found a significantly higher frequency of concordance for the 2255 MZ pairs regarding angina pectoris[42]

In the present study the prevalence of manifest CHD was about 5 per cent which is about the same as for the Tecumseh population Since the series was small it was impossible to draw definitive conclusions regarding heredity and CHD in this form

To be able to diagnose also silent CHD and thus to approach closer to the true prevalence of this disease, which according to autopsy studies is about 20 per cent[3, 150] it was chosen in the present investigation to perform exercise tests and assess the segmental ST depressions in connection with exercise There is still some uncertainty as to the reliability of this test but there is evidence from certain studies that it is fairly high (p 42)

From the analysis of these post exercise ST segment depressions for the pairs both members of which gave valid ECGs it was evident that the observed coincidence frequency definitely exceeded the expected value but that the differences were of the same order for DZ and MZ This would mean that segmental ST depressions of at least 0 5 mm, which was considered to indicate silent CHD would be largely due to environmental factors or multiple dominant genes The latter explanation is the more likely since the dizygotic pairs also displayed a significantly higher coincidence

BLE 29 *Correlations between systolic blood pressure and anthropometric parameters*

	MZ				DZ			
	Intrasubject	Cross 1	Cross 2		Intrasubject	Cross 1	Cross 2	
	r	*r*	*r*	*n*	*r*	*r*	*r*	*n*
				MALES				
tolic pressure versus								
ge	0.255*	0.255*	0.354**	59	0.254*	0.254*	0.379**	60
iastolic pressure	0.634***	0.521***	0.357**	59	0.796***	0.392**	0.319*	60
eight	0.082	−0.011	0.075	59	0.148	0.148	0.238	60
kinfold triceps area	0.289*	0.146	0.256*	59	0.129	0.117	0.198	60
pper arm circumference	0.066	−0.006	−0.050	59	0.053	0.043	0.221	60
eart volume	0.172	0.075	0.215	59	0.364**	0.106	0.341**	60
				FEMALES				
tolic pressure versus								
Age	0.428*	0.4[illegible]8*	0.495**	33	0.630***	0.630***	0.593***	44
Diastolic pressure	0.768***	[illegible].577***	0.661**	33	[illegible].642***	[illegible].593***	[illegible].248	44
Weight	0.229	0.360*	−0.027	33	0.293	0.389**	0.091	44
Skinfold triceps area	0.135	0.200	−0.020	33	0.129	0.247	−0.122	44
Upper arm circumference	0.242	0.360*	−0.003	33	0.280	0.347*	0.132	44
Heart volume	0.398*	0.517**	0.230	33	0.460*	0.459**	0.113	44

Symbols: * $P < 0.05$; ** < 0.01; *** < 0.001

The intra subject correlation and one cross twin correlation between the systolic pressure and skinfold thickness in the triceps area were significant ($P < 0.05$) for MZ but not for DZ. The relationship was thus probably due to genetic factors but as a comparison between cross twin for MZ and cross twin for DZ by a z transformation disclosed no significance the correlation may have its explanation in physiologic or technical factors.

In the DZ group there were significant intra subject and cross-twin correlations between systolic pressure and heart volume but since this was not found in the MZ group it was probably due to physiologic factors.

In the women both the intra subject and cross twin correlations of systolic blood pressure with diastolic pressure and heart volume were significant for MZ and DZ. The correlations between these variables were therefore due chiefly to physiologic factors. One of the cross twin correlations of systolic pressure with weight and skinfold thickness was significant at the 5 per cent level in both MZ and DZ groups. The intra subject correlations showed the same tendency but not at the 5 per cent level. These associations were therefore most probably due to technical and/or physiologic factors.

Comments

The observed strong genetic influence of the variability of both systolic and diastolic pressures [illegible] in full agreement with the findings in twin studies by Osborne

TABLE 27 Basal diastolic pressure, mean variances

	Male				Female			
	n	Variance	*F*	*P*	*n*	Variance	*F*	*P*
MZ_{ia}	59	60.0			33	29.8		
DZ_{ia} MZ_{ia}			1.76	< 0.05			4.82	< 0.001
DZ_{ia}	60	105.6			44	143.5		
DZ_{ir} DZ_{ia}			2.33	< 0.01			1.93	< 0.05
DZ_{ir}	60	122.9			44	138.4		
MZ_{ir} MZ_{ia}			2.76	< 0.001			5.70	< 0.001
MZ_{ir}	59	77.9			33	84.9		

Symbols as for table 26

Diastolic blood pressure (table 27) — The variance analyses for the diastolic blood pressure yielded almost identical values to the systolic, this indicates that the variability of diastolic pressure is predominantly under genetic influence

(b) Elevated diastolic blood pressure

In the monozygotic group the differences between the expected and observed coincidence frequencies were significant ($P < 0.05$) irrespective of the blood pressure level chosen (90 or 95 mm Hg)

In the dizygotic group a significant difference between the expected and observed coincidence frequencies was obtained only for the lower pressure (table 28)

(c) Relation to age and anthropometric measurements (table 29)

In the men the systolic pressure showed significant correlation with age both in the MZ and DZ groups The intra subject correlation between systolic and diastolic pressures was significant as was the cross twin correlations This indicates that the correlations found were due mainly to physiologic factors

TABLE 28 Prevalence and expected and observed coincidence frequencies for elevated diastolic pressures (n, number of pairs)

	Diastolic blood pressure	Prevalence %	Expected coincidence *n*	Expected coincidence %	Observed coincidence *n*	Observed coincidence %	*P*
MZ	≧ 90 mm Hg	10.3	1	1.1	4	4.4	< 0.05
$n = 92$	≧ 95	6.0	0	0.4	3	3.3	< 0.05
DZ	≧ 90 mm Hg	20.2	4	4.1	12	11.5	< 0.001
$n = 104$	≧ 95	9.1	1	0.8	3	2.9	> 0.05

SERUM LIPIDS, SMOKING AND HEREDITY

by

Rolf Blomstrand and Torbjörn Lundman

Introduction

It has been firmly established that an elevated level of cholesterol in human serum is associated with a high prevalence of coronary heart disease.[129] Biorck, Blomquist & Sievers [illegible] among others have found higher cholesterol values in younger than older cases of myocardial infarction. These findings were confirmed and extended in the Framingham study.[49] There is also much evidence that in cases of essential familial hypercholesterolaemia the incidence of coronary heart disease is high.[129]

In recent years methods for determining serum triglycerides have been available and it has been shown that high levels of these are associated with coronary heart disease. *In 1959 Albrink & Man reported that the* triglycerides were more often elevated in cases of coronary heart disease than in healthy subjects.[6] A similar result was reported by Carlson[36] who found a significantly elevated level of triglycerides in men below 50 years with myocardial infarction. Essential familial hyperglyceridaemia is another metabolic disorder probably inherent that is accompanied by a clinical syndrome including coronary heart disease.[139]

Investigations have been published in which *an association has been found be*tween high serum lipid levels and smoking. Gofman Lindgren Strisower DeLalla Glazier & Tamplin[72] found that certain lipoproteins and cholesterol were elevated and the same was noted for cholesterol in the *Framingham 6-year follow up study*.[50]

Associations have thus been found between smoking and CHD, between CHD and cholesterol and between cholesterol and smoking. Since the relationship between cholesterol and CHD is probably causal the other two relations could be a pure coincidence provided that the higher prevalence of CHD in smokers can be ascribed to constitutional differences. From the results *in the earlier part of this investigation it* would seem that there was no excess morbidity from cardiovascular disease in the co-twins more exposed to smoking. It was therefore considered that a serum lipid study *on the twins discordant with respect to* smoking in the present series (77 monozygotic, 89 dizygotic) might throw more light on these problems. Such a study was prompted also by the fact that the nicotine absorbed on smoking 1—3 cigarettes has acute effects on the lipid metabolism.[92, 93]

From twin studies conducted by Osborne, Adlersberg, DeGeorge & Wang,[114] Meyer[109] and Jensen Blankenhorn Chin, Sturgeon & Ware[86] evidence has been adduced for both a genetic and environmental *influence on cholesterol, triglyceride and* phospholipid levels. As the twins examined by these workers were usually young, it was considered of great interest to examine in the present series the relative importance

De George & Mathers[115] and Takkunen[143] The stronger effect of heredity for the females was also found by Osborne *et al*

While there is thus no doubt regarding the influence of heredity on the variability of the blood pressure over the full range, the causal significance of heredity to hypertension is more difficult to elucidate On the basis of, for instance, a study on twin pairs Platt has proposed that hypertension is a hereditary disease and he has formulated a theory based on the action of a single gene with incomplete dominance[118] The present results relating to the elevated diastolic pressure are compatible with this theory The frequency distribution curve of blood pressure in the present series was, however, normal and multifactorial influences thus cannot be ruled out It is probable that the importance of genetic factors was to some extent underestimated, because many of the pairs were discordant with respect to smoking and the smoking co twin usually had a lower blood pressure A clearer impression of the importance of hereditary factors would be obtained from a twin series of concordant non smokers

The associations found between the systolic blood pressure and a number of anthropometric variables were due mainly to physiologic factors as shown by the cross twin analyses The observed correlation with age, diastolic pressure, skinfold thickness and heart volume is a known physiologic fact[22]

TABLE 31 Serum lipids in relation to smoking exposure

		Males			Females		
		$\bar{y}$	±S E	r	$\bar{y}$	±S E	r
		MONOZYGOTIC PAIRS					
Discordance group							
A	Cholesterol mg/100 ml	2 9	±7 3	—0 098	2 6	±10 3	—0 320
♂ 44	Triglycerides	—1 9	±8 2	—0 024	—0 4	±6 1	—0 116
♀ 32	Phospholipids	—2 1	±5 7	0 110	6 7	±8 9	—0 126
B	Cholesterol	—9 7	±14 0	0.222	—8 7	±10 7	—0 154
♂ 17	Triglycerides	—9 0	±13 5	—0 063	+2 8	±7 8	—0 161
♀ 20	Phospholipids	—2 9	±9 6	0 239	—5 2	±9 4	0 226
		DIZYGOTIC PAIRS					
Discordance group							
A	Cholesterol	1 4	±8 9	0 094	—1 3	±10 5	—0 016
♂ 51	Triglycerides	8 4	±10 0	0 298	3 9	±9 5	0 103
♀ 36	Phospholipids	13 0	±7 6	0 184	13 7	±11 0	0 266
B	Cholesterol	8 8	±9 8	—0 073	3 4	±10 5	—0 046
♂ 26	Triglycerides	0 7	±10 9	—0 162	6 1	±10 0	0 098
♀ 34	Phospholipids	11 0	±9 4	0 030	16 8	±11 6	0.245

Symbols as for table 7

To test the reproducibility of the method a sample of pooled serum was analysed at regular intervals The mean for the 20 samples analysed in this way was 263 mg/100 ml. The standard deviation for a single determination was ±6 7 mg/100 ml

Serum lipids in relation to smoking

The twin sample is described by the means for cholesterol triglycerides and phospholipids for MZ and DZ men and women (table 30) The values are based on one member of each pair

The *results of the analyses of correlation* between the intra pair differences for serum lipids and the intra pair difference for cigarette consumption are given in table 31

Monozygotic group — The 44 male and 32 female pairs in *discordance group A* gave values near zero for the mean intra pair difference for the 3 lipids analysed For the female pairs there were also con sistently negative correlations suggesting an association between cigarette consumption and the reduction in the lipid levels For cholesterol the negative correlation was significant at the 10 per cent level

If the calculation was performed on *discordance group B* — that is pairs com prising one smoker and one non smoker — negative values for the mean intra pair difference were almost invariably found suggesting that the levels of cholesterol triglycerides and phospholipids were on average lower for the more exposed co-twins. The differences were not significant however Likewise *there was no significant* correlation between the lipid levels and cigarette consumption. The findings are shown graphically in figure 7

of the environmental and genetic components on the variability of the 3 lipid classes and on their interrelationships The analysis of variance as performed by Osborne & DeGeorge was used[113] Here, a comparison is made between the mean intra pair variances for MZ and DZ and between the mean intra and inter pair variances A strong genetic component would reduce the mean intra pair variance for MZ in relation to that for DZ. For studying the interrelationships between the 3 lipid classes the cross twin analysis evolved by Osborne & De George is the most convenient method and was therefore used[113]

Methods for determining serum lipids

When all the samples had been collected determinations of cholesterol, triglycerides and phospholipids were made

Cholesterol was determined after the serum protein had been precipitated with isopropyl alcohol by a method reported by Zak, Dickenman, White, Burnett & Cherney[151] The determinations were performed on an autoanalyzer[a]

To test the reproducibility of the method a sample of pooled serum was analysed at regular intervals The mean for the 9 samples analysed in this way was 259 mg/100 ml The standard deviation for a single determination was ±5 0 mg/100 ml

Triglycerides were determined, after extraction of total lipids with a mixture of chloroform and methanol (2 1 v/v) by a method evolved by Blankenhorn, Rouser & Weimer[25]

To test the reproducibility of the method a sample of pooled serum was analysed at regular intervals The mean for the 28 samples analysed in this way was 285 mg/100 ml The standard deviation of a single determination was ±12 0 mg/100 ml

Phospholipids were determined directly by assaying lipid phosphorus with a method reported by Bartlett[15] The final stage of the determination, namely, the reading of the extinction at 830 mμ was performed on an autoanalyzer[a] The correction factor of 25 was used to calculate the amount of phospholipids in milligrammes per 100 millilitres

[a] Technicon Instruments Corporation New York

TABLE 30 Means for cholsterol triglycerides and phospholipids with respect to sex and zygosity (Based on one member of each pair)

	MZ		DZ	
	Males $n = 58$	Females $n = 33$	Males $n = 60$	Females $n = 42$
	M±S E S D	M±S E S D	M±S E S D	M±S E S D
Cholesterol, mg/100 ml	294±7 1 *54 5*	313±10 1 *58 2*	295±7 5 *57 9*	312±7 5 *48 8*
Triglycerides	182±10 0 *75 8*	147±7 3 *41 7*	167±9 3 *72 2*	157±8 5 *54 9*
Phospholipids	288±6 8 *51 7*	303±9 0 *51 9*	280±6 4 *49 6*	305±7 4 *47 7*

The results for the DZ group are largely in agreement as regards *cholesterol and* triglycerides The phospholipids were however elevated in smokers in the dizygotic group Since the results for the monozygotic group do not indicate the presence of any association with smoking, this would seem to reflect a constitutional difference between *smokers and non smokers*

From the results reported above it is evident that the smoking co-twins had a slightly lower weight and reduced skinfold thickness measured in the triceps area. *Since skinfold thickness and at least the* triglyceride level are known to be correlated[12] the findings as regards smoking and the serum lipids are hardly unexpected

As mentioned earlier smoking exerts an acute effect on the lipid metabolism Kershbaum *et al* found that the nicotine absorbed in smoking a few cigarettes most probably through catecholamine liberation produces a rise in the free fatty acids in serum[92, 93] After prolonged administration of nicotine in the dog these authors also found a 50 per cent rise in the cholesterol level[94]

Studies of the acute effect of smoking on other lipid fractions than free fatty acids in man have yielded diverging results Page Lewis & Moinuddin found no effect on the cholesterol level of habitual smokers and non smokers after rapid smoking of 2 cigarettes[116] Examining 20 young men who smoked for 5 hours after a fatty meal and 20 who did not smoke Konttinen & Rajasalmi found a smaller rise in triglycerides in *the* smokers[97] *The free fatty acids* showed a non significant increase in the smokers while the cholesterol level was unchanged Butkus & Page examined the cholesterol, triglycerides and phospholipids after 4 hours intensive smoking and after a control period without smoking and found

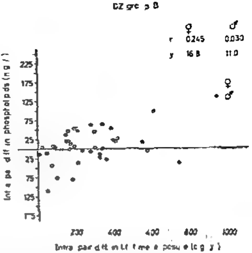


Figure 8 Correlation between smoking exposure and phospholipids for DZ, discordance group B

no significant difference between the means[34]

The association between smoking and mortality from CHD and the acute effects on the lipid metabolism due to smoking has led to the conclusion that cigarette smoking over a long period increases the cholesterol level.[92] It is inferred by Gofman *et al*[72] and Bronte Stewart[30] from their results that there is such an association. In the Framingham study too higher cholesterol values were recorded for smokers[50] In a study of a Finnish male population by Karvonen, Orma, Keys Fidanza & Brozek on 360 smokers and 165 non smokers aged 20—59 years higher average cholesterol values were also found in the former[90] On the other hand, *normal* cholesterol values were found by Acheson & Jessop[2] in smoking men aged 65—80 years and by Konttinen[96] in 314 men between 18 and 25 years. In an investigation on about 6000 persons *in a health examination* Carlson & Lindstedt found in contrast to the results of the present investigation,

Dizygotic group — For the 51 male and 36 female pairs the mean intra pair differences and correlations for cholesterol and triglycerides differed negligibly from zero

As regards the phospholipids, however, there were positive values for the mean intra pair difference in both the male and female groups, which suggests that the phospholipid level was on average higher for the more exposed co-twins The differences were not significant ($P > 0\,05$)

In *discordance group B* the deviation of the mean intra pair difference from zero was negligible for both cholesterol and triglycerides, but not for the phospholipids (figure 8) When the sexes were combined, a significantly positive value was obtained for the mean intra pair difference ($\bar{\zeta} = +14\,3$ mg/100 ml $P < 0\,05$)

Comments

From the results for the MZ group it was evident that prolonged smoking has only an insignificant effect on the lipid levels in serum If there is any correlation at all between the lipids and cigarette consumption it is a negative one so far as cholesterol and triglycerides are concerned In a comparison between the mean intra pair difference for the 3 classes of lipids in *discordance group A* which included pairs both members of which were smokers, and *discordance group B* (pairs comprising one smoker and one non smoker), the negative tendency was well defined This tendency rather than the level of significance of their respective values would suggest that smoking is associated with a reduction in cholesterol and triglycerides

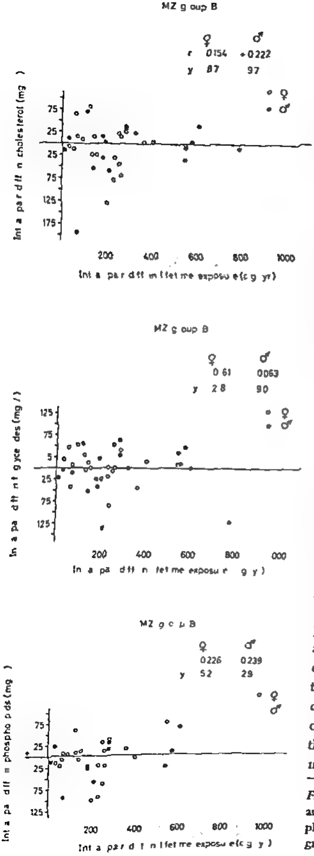


Figure 7 Correlation between smoking exposure and cholesterol (top) triglycerides (middle) and phospholipids (bottom) for MZ, discordance group B

The results for the DZ group are largely in agreement as regards cholesterol and triglycerides. The phospholipids were however elevated in smokers in the dizygotic group. Since the results for the monozygotic group do not indicate the presence of any association with smoking, this would seem to reflect a constitutional difference between smokers and non smokers.

From the results reported above it is evident that the smoking co-twins had a slightly lower weight and reduced skinfold thickness, measured in the triceps area. Since skinfold thickness and at least the triglyceride level are known to be correlated[12] the findings as regards smoking and the serum lipids are hardly unexpected.

As mentioned earlier smoking exerts an acute effect on the lipid metabolism. Kershbaum *et al.* found that the nicotine absorbed in smoking a few cigarettes most probably through catecholamine liberation produces a rise in the free fatty acids in serum.[92, 93] After prolonged administration of nicotine in the dog these authors also found a 50 per cent rise in the cholesterol level.[94]

Studies of the acute effect of smoking on other lipid fractions than free fatty acids in man have yielded diverging results. Page, Lewis & Moinuddin found no effect on the cholesterol level of habitual smokers and non smokers after rapid smoking of 2 cigarettes.[116] Examining 20 young men who smoked for 5 hours after a fatty meal and 20 who did not smoke Konttinen & Rajasalmi found a smaller rise in triglycerides in the smokers.[97] The free fatty acids showed a non significant increase in the smokers while the cholesterol level was unchanged. Butkus & Page examined the cholesterol, triglycerides and phospholipids after 4 hours intensive smoking and after a control period without smoking and found

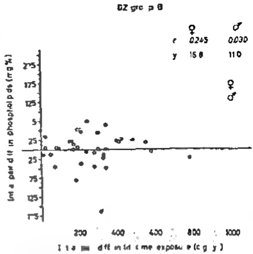


Figure 8. Correlation between smoking exposure and phospholipids for DZ, discordance group II.

no significant difference between the means.[34]

The association between smoking and mortality from CHD and the acute effects on the lipid metabolism due to smoking has led to the conclusion that cigarette smoking over a long period increases the cholesterol level.[92] It is inferred by Gofman *et al.*[72] and Bronte Stewart[30] from their results that there is such an association. In the Framingham study too higher cholesterol values were recorded for smokers.[50] In a study of a Finnish male population by Karvonen, Orma, Keys, Fidanza & Brozek on 360 smokers and 165 non smokers aged 20—59 years higher average cholesterol values were also found in the former.[90] On the other hand normal cholesterol values were found by Acheson & Jessop[2] in smoking men aged 65—80 years and by Konttinen[96] in 314 men between 18 and 25 years. In an investigation on about 6000 persons in a health examination Carlson & Lindstedt found in contrast to the results of the present investigation

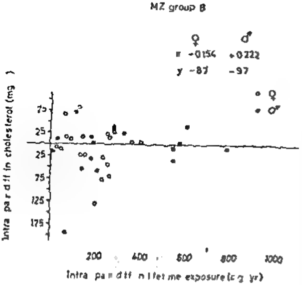
Dizygotic group — For the 51 male and 36 female pairs the mean intra pair differences and correlations for cholesterol and triglycerides differed negligibly from zero

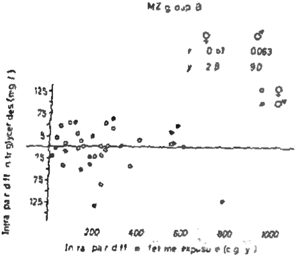
As regards the phospholipids, however, *there were positive values for the mean intra pair difference in both the male and female groups, which suggests that the phospholipid level was on average higher* for the more exposed co-twins The differences were not significant ($P > 0\cdot05$)

In discordance group B the deviation of the mean intra pair difference from zero was negligible for both cholesterol and triglycerides, *but not for the phospholipids* (figure 8) When the sexes were combined, a significantly positive value was obtained *for the mean intra pair difference* ($\bar{y}$ = $+14\cdot3$ mg/100 ml $P < 0\cdot05$)

Comments

From the results for the MZ group it was evident that prolonged smoking has only an insignificant effect on the lipid levels in serum. If there is any correlation at all between the lipids and cigarette consumption it is a negative one so far as cholesterol and triglycerides are concerned In a comparison between the mean intra pair difference for the 3 classes of lipids in *discordance group A* which included pairs both members of which were smokers and *discordance group B* (pairs comprising one smoker and one non smoker) the negative tendency was well defined This tendency rather than the level of significance of their respective values would suggest *that smoking is associated with a reduction in cholesterol and triglycerides*





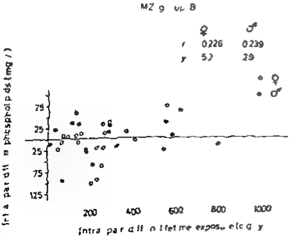


Figure 7 Correlation between smoking exposure and cholesterol (top) triglycerides (middle) and phospholipids (bottom) for MZ, discordance group B

TABLE 33 Triglycerides mean variances

	Male				Female			
	n	Variance	*F*	*P*	*n*	Variance	*F*	*P*
ME	[illegible]	144 0			28	144 0		
MZ_{ia} ME			11 8	< 0 001			6 1	< 0 001
MZ_{ia}	58	1790 0			33	728 6		
DZ_{ia} MZ_{a}			1 32	> 0 05			2 09	< 0 05
DZ_{ia}	60	2240 9			42	1525 5		
DZ_{r} DZ_{a}			2 80	< 0 001			2 76	< 0 01
DZ_{ir}	60	3135 7			42	2108 5		
MZ_{r} MZ_{ia}			5 17	< 0 001			2 53	< 0 01
MZ_{ir}	58	4397 1			33	923 3		

Symbols as for table 26

age group 38—47 showed F ratios of the same magnitude

Triglycerides (table 33)

For both sexes the values for the mean intra pair variance were lower for MZ than DZ, but the F ratio was significant only for female group (P < 0 05) Both MZ and DZ mean inter pair variances were significantly higher than the mean intra pair variances These results suggest that the variability of the triglyceride level con tains both genetic and environmental com ponents The genetic ones are probably

TABLE 34 Phospholipids mean variances

	Male				Female			
	n	Variance	*F*	*P*	*n*	Variance	*F*	*P*
ME	20	44 8			20	44.8		
MZ_{ia} ME			19 4	< 0 001			27 2	< 0 001
MZ_{ia}	[illegible]	871 1			33	1222 0		
DZ_{ia} MZ_{ia}			1 63	< 0 05			1 76	< 0 05
DZ_{ia}	60	1425 2			42	2145 2		
DZ_{r} DZ_{ia}			1 96	< 0 01			1 62	> 0 05
DZ_{ir}	60	1399 8			42	1740 2		
MZ_{ir} MZ_{ia}			4 41	< 0 001			3 58	< 0 001
MZ_{ir}	58	1921 2			33	2188 3		

Symbols as for table 26

that the triglyceride levels were elevated in smokers.[37]

As intimated above, it remains to be ascertained whether the elevation in cholesterol in smokers found by a number of authors is due to smoking or to constitutional differences between smokers and non-smokers. The negative results obtained in the present study as regards cholesterol and triglycerides support the constitutional theory. Further verification is provided by the fact that the dizygotic but not monozygotic smokers had higher phospholipid values than the non-smokers.

If the higher cholesterol level in smokers found in some prospective studies can be ascribed to constitutional differences between smokers and non-smokers, we may have here one explanation of the reported excess mortality for coronary heart disease.

Genetic considerations

Variability of serum lipid levels

Analyses of variance for the various serum lipids were performed on the whole twin sample consisting of 196 pairs aged 38—77 years, and on the youngest age group (38—47 years) consisting of 74 pairs. No pair was excluded owing to illness or elevated lipid values. In 3 out of the 196 pairs no blood sample was obtained (1 MZ, 2 DZ).

Cholesterol (table 32)

The F ratio between the mean variance for the measurement error and the MZ mean intra-pair variance was statistically significant ($P < 0.001$), the reliability of the cholesterol method was thus entirely acceptable. The mean intra-pair variance for DZ was higher than that for MZ but not significantly so. The mean inter-pair variances however were significantly higher than the corresponding intra-pair variances. This shows that the variability of the cholesterol level in serum of subjects aged 38—77 years is determined by both genetic and environmental factors. No sex difference was noted.

An analysis of variance performed on the

TABLE 32 Cholesterol mean variances

	Male				Female			
	n	Variance	F	P	n	Variance	F	P
ME	9	25.0			9	25.0		
MZ_{ia} ME			63.6	< 0.001			64.0	< 0.001
MZ_{ia}	58	1590.1			33	1597.8		
DZ_{ia} MZ_{ia}			1.10	> 0.05			1.54	> 0.05
DZ_{ia}	60	1755.8			42	2461.1		
DZ_{ir} DZ_{ia}			2.71	< 0.001			1.96	< 0.05
DZ_{ir}	60	2381.1			42	2408.0		
MZ_{ir} MZ_{ia}			2.58	< 0.001			3.70	< 0.001
MZ_{ir}	58	2048.7			33	2958.8		

Symbols as for table 26

TABLE 56 *Correlations between the various serum lipids*

	MZ				DZ			
	Intrasubject *r*	Cross 1 *r*	Cross 2 *r*	*n*	Intrasubject *r*	Cross 1 *r*	Cross 2 *r*	*n*
MALES								
Cholesterol versus								
Triglycerides	0 419***	0 151	0 217	58	0 498***	0 232	0 217	60
Phospholipids	0 680***	0 488***	0 285*	58	0 665***	0 415***	0 338**	60
Triglycerides versus								
Phospholipids	0 381**	0 26[illegible]*	0.207	58	0 339 **	0 339**	0 256	60
FEMALES								
Cholesterol versus								
Triglycerides	0 497**	0 341*	0 194	33	0 235	0 023	0 021	4
Phospholipids	0 8[illegible]4***	0 398*	0 625***	33	0 667***	0 263	0 362*	4
Triglycerides versus								
Phospholipids	0 499 *	0 199	0 316*	33	0 365*	0 181	0 05	4

Symbols * P < 0 05
** < 0 01
*** < 0 001

was significant for men and women. In the absence of any difference between MZ and DZ cross twin correlations the observed association was probably due largely to physiologic factors

Comments

Variability of serum lipid levels

The variability of cholesterol in the age group 37—78 years would seem to be due both to environmental and genetic factors That other workers have obtained different results may be ascribed to the age factor A strong genetic component was found by Gedda & Poggi[68] in their study on 50 monozygotic and 50 dizygotic twins aged 6—19 years similar results were obtained by Meyer[109] for 26 monozygotes and 29 dizygotes most of them aged 10—19 years and by Jensen *et al*[86] who examined 31 monozygotes and 17 dizygotes ranging in age from 16 to 79 years However in a study on cholesterol and triglycerides conducted by Osborne *et al*[114] on [illegible] pairs aged 18—55 years the F ratios between the DZ and MZ mean intra pair variances were in close agreement with those of the present study Osborne s series however, excluded all pairs with any disease or lipid values beyond the 95th percentile point. That is in the higher age groups the genetic factors are hard to discern

As regards the phospholipid level a strong genetic influence was found in the present study and this accords with the results reported by Jensen *et al*[86] Vikrot found that under normal conditions the phospholipid level is constant but that it varies widely during pregnancy probably owing to hormonal adjustments[148] It is conceivable that the regulatory mechanism for phospholipids in serum is *entirely different* from that for cholesterol and triglycerides

stronger so far as the women are concerned The same applies to the age group 37—48 years

Phospholipids (table 34)

For both sexes a significant F ratio was noted between the DZ and the MZ mean intra pair variances This indicates that the variability of the phospholipid level is determined largely by heredity The analysis of variance performed on the age group 38—47 gave almost identical F ratios

Lipid levels and age (table 35)

As the distribution of the triglycerides was skew, common logaritms of these values were used [35]

In the male monozygotic group there was only a weak association between age and serum lipid levels In the female groups, however, highly significant correlations were found, especially for the monozygotes

Correlation between the various lipids

(table 36)

For the men in both MZ and DZ groups significant intra subject correlations of cholesterol with triglycerides and phospholipids were found Thus, since there were significant cross twin correlations for both MZ and DZ, the association was probably due mainly to physiologic factors

For the women, too, the intra subject correlations were at the level of significance, except that between cholesterol and triglycerides in the DZ group In view of the significant MZ cross twin correlation between these two lipids, it is possible that this association is in some measure of hereditary origin The intra subject correlation between triglycerides and phospholipids

TABLE 35 Correlations between age and serum lipids

	MZ			DZ		
	Twin A	Twin B		Twin A	Twin B	
	r	r	n	r	r	n
			MALES			
Age versus						
Cholesterol	0 278*	0 108	58	0 076	−0 039	60
Triglycerides	0 220	0 164	58	0 168	0 188	60
Phospholipids	0 208	0 157	58	0 096	0 096	60
			FEMALES			
Age versus						
Cholesterol	0 493**	0 590***	33	0 294	0 214	42
Triglycerides	0 357*	0 412*	33	0 331*	0 413**	42
Phospholipids	0 506**	0 454**	33	0 356*	0 086	42

Symbols * $P < 0\,05$
** $< 0\,01$
*** $< 0\,001$

ɪLE 36 . *Correlations between the various serum lipids*

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	Intrasubject r	Cross 1 r	Cross 2 r	n	Intrasubject r	Cross 1 r	Cross 2 r	n
MALES								
olesterol versus								
riglycerides	0 419***	0 151	0 217	58	0 498***	0 232	0 217	60
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glycerides versus								
hospholipids	0 381**	0 [illegible]62	0[illegible]07	58	0 539***	0 339**	0 256	60
FEMALES								
olesterol versus								
Triglycerides	0 497**	0 341*	0 194	33	0 235	0 023	0 021	42
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Symbols * $P < 0\ 05$
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Of the environmental factors that exert an influence upon the lipid level, diet is known to be one of the most important In the above mentioned studies by Osborne *et al* [114] and Meyer[109] a lower mean intra pair variance was found for the pairs living together than for those living apart, this indicates the great importance of such environmental factors The pairs in the present series had lived apart for the latter part of their life and this implies that the lipid level could be affected more strongly by different environmental factors

The relation between lipid levels and age

The positive correlation between the serum lipids and age showed a definite sex difference, it being weak or nil in the male groups but strong among the women Such a sex difference was found for cholesterol and phospholipids also by Adlersberg, Schaefer, Steinberg & Wang, in whose material of 1200 men and women between 2 and 77 years the lipid levels increased for the men up to 33 years and for the women up to 58 years [4] Carlson found a clear age correlation also for triglycerides in men up to 40 years [35] That the women showed a rise in the lipid levels with age even after 40 years is probably due to the hormonal adjustment at the menopause [62]

Correlation between the various lipids

Between the various classes of lipids and especially between cholesterol and phospholipids there was a strong association and for both men and women This has been observed by other workers Carlson[35] found a significant correlation between the above serum lipids in 151 men aged 26—73 in good health, and Cramer[45] reported a similar relationship for 15 men and 15 women The cross twin analysis in the present study showed that these associations were due mainly to physiologic factors

Summary

In a co twin control study on 77 monozygotic and 89 dizygotic twins discordant with respect to smoking an examination has been made of the association between cigarette smoking and the serum lipids cholesterol triglycerides and phospholipids The cholesterol and triglyceride levels were lower for the smoking monozygotic twins than for the non smoking co-twins but the differences were not significant. The phospholipid level was significantly higher for the smoking dizygotic co-twins These results would seem to support the theory that smokers and non smokers have constitutional differences

The relative importance of genetic and environmental factors to the variability of the serum lipid levels was examined on the whole twin sample, consisting of 196 pairs aged 37—78 years (92 MZ and 104 DZ) As regards cholesterol these factors were of fairly equal strength while for triglycerides and phospholipids the genetic component was the stronger The rise in the lipid levels with age was insignificant in the male group but pronounced among the women The association between the various lipids was examined by cross twin analysis The strong interrelationships observed were due to physiologic factors rather than to heredity

GENERAL DISCUSSION

It would seem tempting to perform quantitative comparisons between the normal population and the present twin series but there are at least two factors that indicate the inadvisability of making such comparisons Firstly it is questionable whether the Swedish Twin Register is representative of the normal population since it comprises only complete pairs[39] The number of broken pairs in a twin population increases rapidly with age until at the highest ages there remain no complete pairs[7] The implication of the exclusion of broken pairs from the Register can be established only by direct comparisons between the two populations Secondly the present series was strongly selected from the aspect of environment Not only was it required that the pairs should be discordant with respect to smoking but for more than one half of their life they should have lived in a large town However the validity of the co-twin control method for examining an environmental factor will probably not be vitiated by any lack of representativeness of the twin population This method has the great advantage that a control subject is obtained that is of the same age sex and constitutional background

As regards the present series the percentage of participants was large for such a material The non response group was carefully analysed as regards manifest disease and a comparison was made with the smoking habit The results of the co-twin control study were probably not distorted by the losses However it should be borne in mind that the series was small

A high prevalence of diseases with a genetic basis in the non response group might result in an underestimate of the significance of heredity as studied by the classical twin method The magnitude of any such underestimate is difficult to ascertain, since only manifest disease could be recorded for the non respondents There are however other disadvantages of this method in determining the heretability In the comparison between monozygotic and dizygotic pairs it is required that the intra pair difference as regards the environmental factors be the same but the known tendency for monozygotic pairs to stick together may result in overestimates of the hereditary factors Whether this applies also to adults is uncertain In the present series the age at separation was the same for the mono- and dizygotic pairs Nor does the classic twin method provide any information on whether recessive or dominant genes are responsible for the observed coincidence The presence of such dominant genes also gives rise to a high coincidence frequency for the dizygotic pairs this may result in underestimation of the heretability since it is required that the monozygotic pairs should display a higher coincidence frequency than the dizygotes

To be able to make an acceptable intra pair comparison as regards coronary heart disease it was necessary to take account *not* only of overt but also of preclinical stages

Of the methods most commonly used in epidemiologic studies and health investigations, the case history and *resting* electro cardiogram are the most important That these are *inadequate for diagnostic purposes* is generally agreed, and *has* been *clearly* demonstrated by Schor *et al*[130, 131] They found that in only 58 per cent *of the* 181 *fatal* cases of coronary heart disease had the disease been diagnosed at the last *periodic* health examination before death

It has been suggested that the exercise test is considerably *more reliable for* diagnosing coronary heart disease[105, 106, 107, 122] *For* this reason, in the present study *segmental* ST depressions of at least 0 5 *mm after* a maximal exercise test were con sidered to *indicate silent coronary* heart *disease*, and depressions less than this were *regarded* as a *borderline* group In men 40—60 *years of age and* in sound health Doan *et al*[52] found a prevalence of about 16 per cent for segmental ST depressions *of at least* 1 *mm* immediately after a maxi mal exercise test, this is in a fairly close agreement with *the frequency of segmental* ST depressions of at least 0 5 mm 3 mi nutes after exercise obtained in the present investigation In *their one year follow up of* 212 men an extremely close reprodu cibility was obtained, none of the 166 subjects recording a normal exercise test at the *first* examination displaying overt coronary heart disease at the follow up

A few of the twins in the present series did not perform the exercise test usually because they had overt coronary heart dis ease, and the diagnosis was then made on the basis of the criteria recommended by the WHO Expert Committee on Arterial Hyper tension and Ischaemic Heart Disease[33]

With these criteria for coronary heart disease no excess morbidity was found for the *smoking* monozygotic co-twins There was, *instead*, a slightly higher frequency of segmental ST *depressions in the* less exposed *group The* most *likely* explanation of this striking result would seem to be that owing to *respiratory complaints* the smoking twins *did* not attain the same level of heart rate as their non smoking *co-twins during* the exercise test.

The question immediately arises whether the intra pair *difference in smoking* exposure *was great* enough for any differences to be expecetd The most *convincing answer* is provided by the results *obtained on the respiratory system First*, the prevalence of respiratory symptoms was significantly greater for the *smoking* co *twins*, and then the lung function tests indicated a more uneven ventilation and greater airway re sistance for these *subjects than for the* non smokers These results are in complete agree ment with and in some cases more con vincing than, those *reported by other* work ers The conclusion reached by the Surgeon General s Advisory Committee on Smoking *and Health that the association is a causal* one was thus confirmed by the present in vestigation[146]

It is evident from the study that smoking over a long period also tends to affect the cardiovascular system in various ways The most *important effect recorded* was a re duction in the basal blood pressure Al though this does not mean that smokers always have a lower *blood pressure it does* show that prolonged smoking of cigarettes does not result in a persistent rise in blood pressure These *findings are in agreement with* those *reported by* Karvonen *et al*[90] Blackburn *et al*[24] and Bronte Stewart[30] In the large follow up study by Hammond & Horn an excess mortality from cerebro-vascular disease was found for smokers[75]

Since this disease is associated with hypertension there was probably a higher incidence of hypertension *among the smokers*. The smoking co-twins tended to be lower in weight probably because of a reduction in the subcutaneous fat this has been found also by *Damon*[48] *and Karvonen et al*.[90] As skinfold thickness is correlated at least with the serum triglyceride level,[12] lower values for the serum lipids would be expected in the smoking co-twins. The analyses in the present study showed only a weak association between smoking and the serum lipids *cholesterol and triglycerides and* this was negative that is to say the cholesterol and triglyceride levels were slightly lower in the smoking co-twins. The Tecumseh study[61] produced similar results but most studies on smoking and mortality from coronary heart disease have disclosed the opposite tendency — *for* instance the Framingham study.[50] Since both high blood pressure and high serum cholesterol and triglyceride levels are associated with coronary heart *disease*[22, 50, 61, 71, 111, 149] the results point indirectly to the absence of a causal association between smoking and coronary heart disease.

A search for a relation between smoking and *morbidity* from coronary heart disease has yielded diverging results probably owing in some measure to the differences in diagnostic criteria. English, Willius & Berkson found that younger smokers had a higher incidence of angina pectoris and myocardial *infarction than non smokers* of the same age.[58] In an examination of 1500 hospital patients with angina pectoris or coronary thrombosis Sigler also found that the age at onset of clinical manifestations was lower for smokers *than non smokers*.[134] *In the* 4- and 6-year follow ups of the Framingham study no hypermorbidity from coronary heart disease was observed for the smoker group.[49, 50] The first report on the combined *Framingham* Albany study published in 1962 showed no connection between smoking and angina pectoris but there was an incidence of myocardial infarction that was *3 times higher for the* smokers [illegible] The second report in 1964 showed no association with morbidity from angina pectoris nor now with myocardial infarction.[56] In the H I P study by Shapiro, Weinblatt, Frank & Sager on the other hand a statistically significant association was found between angina pectoris and smoking in persons aged 35—64 years.[133] Against this evidence stand the results from the Tecumseh study by Epstein, Ostrander, Johnson, Payne, Hayner, Keller & Francis in which a slightly lower prevalence of coronary heart disease (angina pectoris and ECG signs of myocardial infarction) was found among the smokers.[61]

As regards the *mortality* from coronary heart disease the findings reveal a more general agreement that smoking and this disease are possibly related. For instance in the Framingham 6-year follow up[50] and the combined Framingham Albany study[55, 56] the smokers showed a significant excess mortality from coronary heart disease. Similar results were found by Hammond & Horn[76] in a 44 month follow up of 187 783 men, and by Doll & Hill,[54] Buechley, Drake & Breslow [illegible] Dorn[57] and Borhani, Hechter & Breslow.[27] The results of the present investigation are not directly comparable with these because different diagnostic methods were used. In the above mentioned studies only overt coronary heart disease, angina pectoris and myocardial infarction were diagnosed. At this stage the disease has a low prevalence and the number of observed cases will be low *even in*

so large series as those in the above mentioned studies, thus no reliable conclusions can be drawn as regards the association between morbidity from coronary heart disease and smoking. The differences between the results of the morbidity and mortality investigations would seem to support the theory that cigarette smoking tends to give rise to acute occlusive or arrhythmic complications in persons already having coronary heart disease. This remains to be proved, from the study by Yaters, Traum, Brown, Fitzgerald, Geisler & Wilcox on 450 autopsy cases it is evident that the terminal coronary attack occurred more often after strenuous than moderate physical activity.[153]

If smoking does not have this acute deleterious effect, how is the association between the mortality from coronary heart disease and smoking reported by so many workers, to be explained? In 1958 Berkson carried out a critical scrutiny of the then available reports on increased mortality from coronary heart disease for smokers.[14] In one of the explanations he proposes that the differences might have a constitutional basis: Persons who are non smokers, or relatively light smokers are the kind of people who are biologically self protective, and biologically this is correlated with robustness in meeting mortal stress for disease generally.

That there is such a constitutional factor operating in the twin population from which the present material was selected has been shown by Cederlof *et al*.[41] The association between smoking and angina pectoris, diagnosed with a mailed questionnaire, was studied from two aspects. The calculations were made on one hand on the monozygotic pairs discordant with respect to smoking (274 male and 264 female) on the other on a population consisting of one member of each pair — 4000 male and 5200 female subjects. In the former group the constitutional factors were kept under control and no difference was obtained between the smoking and non smoking co-twins as regards the prevalence of angina pectoris. In the latter group, however, where the constitutional factors were not controlled, there was a significant excess morbidity from angina pectoris, at least for the smoking men. The significantly higher phospholipid level in serum found for the smoking dizygotic co-twins but not for the monozygotic pairs in the present series is indicative of the same trend.

Now, if there is a constitutional difference between smokers and non smokers is it great enough to account for the difference between these groups in the morbidity and mortality from coronary heart disease? It is true that there are a number of family studies in which evidence of a genetic component in coronary heart disease has been adduced, but because of the difficulty of making an unbiased selection of controls in such studies and the uncertainty inherent in the diagnostic methods the conclusion could be incorrect.[125, 127, 144, 145]

The present findings indicate the presence of a genetic factor in coronary heart disease and related parameters — for instance as regards the variability of the blood pressure, serum cholesterol, triglycerides and phospholipids. Arcus lipoides corneae which has been found to be more common in young hypercholesterolaemics[64] and arteriosclerotics[129] proved to have a definite genetic component, while there was no association between smoking and this symptom. In the present study the strongest evidence of a genetic factor in coronary heart disease was provided by the high

coincidence frequency as regards the post exercise ST depressions The importance of the genetic influence on coronary heart disease is also underlined by the results obtained by Cederlöf *et al*[42] who in an investigation of the whole twin population found that monozygotic twins were more often concordant with respect to angina pectoris diagnosed on the basis of a mailed questionnaire than were dizygotic twins The results of the present study concerning heredity and coronary heart disease provides a basis for the theory that constitutional differences between smokers and non smokers can give rise to excess morbidity and excess mortality from coronary heart disease in smokers

To avoid those sources of error inherent in the cross-sectional study that are due chiefly to the unreliability of the available clinical methods the present investigation is being supplemented with a mortality study on the whole twin population An essential part of this longterm study is a follow up of the present series that promises to throw more light on the much debated association between mortality from coronary heart disease and smoking

The conclusions that would appear to be justified by the results obtained so far are the following

(1) Cigarette smoking gives rise to a significant increase in the respiratory symptoms of chronic bronchitis an increase in the unevenness of ventilation measured by nitrogen washout, and an increase in airway resistance as measured by dynamic spirometry

(2) Cigarette smoking is probably not associated with coronary heart disease whether of the overt or of the silent form diagnosed by means of the postexercise electrocardiography

(3) Cigarette smoking most probably does not result in persistent hypertension During abstinence the blood pressure is lower for smokers than non smokers

(4) Cigarette smoking seems not to produce any elevation of the serum cholesterol or triglyceride levels On the contrary there is some evidence that the levels are lower for smokers than for non smokers

(5) There is reliable evidence of a significant genetic component in coronary heart disease and related parameters

so large series as those in the above mentioned studies, thus no reliable conclusions can be drawn as regards the association between morbidity from coronary heart disease and smoking The differences between the results of the morbidity and mortality investigations would seem to support the theory that cigarette smoking tends to give rise to acute occlusive or arrhythmic complications in persons already having coronary heart disease This remains to be proved, from the study by Yaters, Traum, Brown, Fitzgerald, Geisler & Wilcox on 450 autopsy cases it is evident that the terminal coronary attack occurred more often after strenuous than moderate physical activity [153]

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of relative load as the non smokers during the exercise test

The levels of the serum lipids cholesterol and triglycerides were on average lower for the smoking monozygotic co-twins but the difference were not significant The smoking dizygotic twins displayed a higher phospholipid level this would suggest the presence of a constitutional difference between smokers and non smokers The smoking twins showed a slight tendency for lower weight probably owing to a reduction in subcutaneous fat

Diastolic hypertension was not more common among the smokers In fact they showed lower basal systolic and diastolic pressures at the time of the examination probably due to abstinence from smoking just before

The significance of genetic factors for overt coronary heart disease could not be reliably assessed owing to the low prevalence (4—5 per cent) Evidence that this disease has a genetic component was found in the silent form diagnosed by means of post exercise electrocardiography

The variability of the systolic and diastolic pressures were found to be genetically determined Correlations were found between the systolic pressure and certain anthropometric parameters and cross twin analysis showed that these correlations were due mainly to physiologic or technical factors

The variability of serum cholesterol was found to be determined by both environmental and genetic factors and that of the triglycerides and phospholipids largely by genetic factors Strong intercorrelations between the various lipids were observed These correlations were due chiefly to physiologic factors

It would seem that the excess morbidity and mortality from coronary heart disease reported in the large prospective studies can be due to constitutional differences between smokers and non smokers

SUMMARY

The principal object of the present study was to examine possibility of a relationship between cigarette smoking and coronary heart disease in a series of monozygotic twins that were discordant with respect to smoking and where the constitutional factors were kept under control. The association between cigarette smoking and lung function, which has been found to be causal, was also studied — mainly to assess whether the exposure was great enough. At the same time it was required to ascertain whether coronary heart disease has a genetic component, for this the classic twin method was used, in which a comparison is made between monozygotic and dizygotic pairs.

The series consisted of 196 pairs, 92 monozygotic and 104 dizygotic like-sexed pairs aged 38—77 years. They composed 79.5 per cent of a sample selected from a twin register comprising some 12,000 pairs compiled at the Department of Hygiene, Karolinska Institute, and the Department of General Hygiene, National Institute of Public Health. The chief selection criterion was discordance with respect to smoking, but the pairs should also be concordant with respect to rural/urban environment: they should have lived more than one half of their life in a large town.

The zygosity was taken as that recorded in the Twin Register (similarity diagnosis), checked against photographic and blood group similarity.

A sociologic and medical history was taken using a cardiovascular questionnaire designed by the London School of Hygiene and Tropical Medicine and a respiratory questionnaire developed by The British Medical Research Council's Committee on the Aethiology of Chronic Bronchitis.

The subjects were submitted to an examination, including blood pressure and anthropometric measurements, a radiographic examination of the heart and lungs, two lung function tests — dynamic spirometry and nitrogen washout by a multiple breath method — and electrocardiographic examinations before, during and after a maximal exercise test. Blood samples were taken after 12—14 hours fast and the serum lipids cholesterol, triglycerides and phospholipids were analysed.

The effect of cigarette smoking on the respiratory system, examined by the co-twin control method, showed that smoking gave rise to a significantly higher frequency of the respiratory symptoms morning cough, chronic cough and morning phlegm.

The degree of uneven ventilation measured by nitrogen washout was correlated with cigarette consumption. The *FVC* and $FEV_{1.0}$ were significantly lower for smokers and there was a correlation with cigarette consumption. The lung function was affected to the same extent in women as in men.

There was no excess morbidity from overt coronary heart disease in the smoking co-twins. The same applies to silent coronary heart disease diagnosed by means of post-exercise electrocardiography. The frequency of segmental ST depressions, on the other hand, was lower for smokers, probably because they did not achieve the same degree

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